

# *The American Journal of* **DIGESTIVE DISEASES**

*An Independent Publication*

**DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION**

**ORIGINAL CONTRIBUTIONS**

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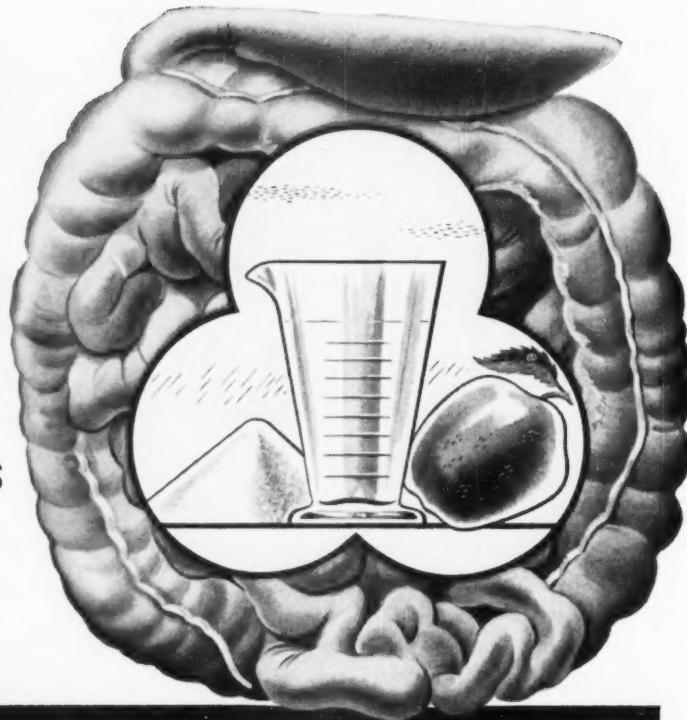
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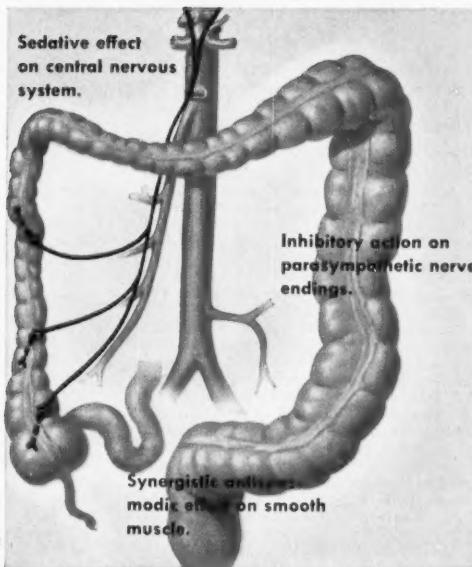
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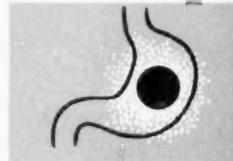
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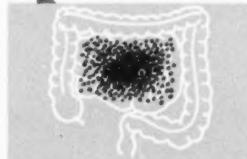
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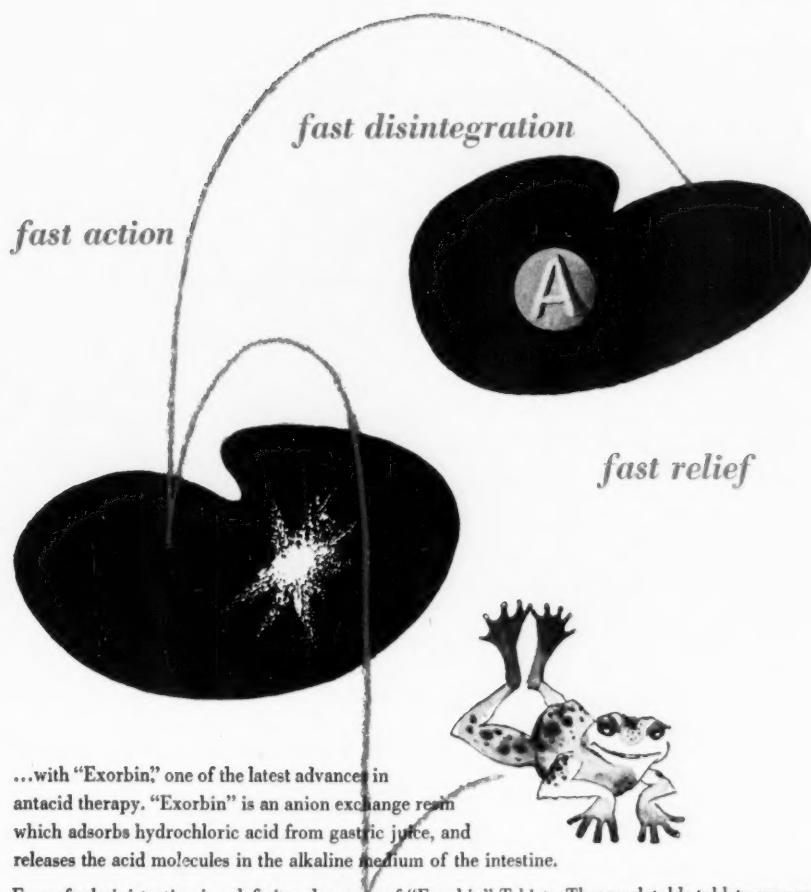
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# PANCREATIC AND GALL BLADDER FUNCTIONS IN PEPTIC ULCER AND CHRONIC ULCERATIVE COLITIS

WM. J. SNAPE, M. D. AND M. H. F. FRIEDMAN, PH.D. Philadelphia, Pa.

THE present paper reports the results of a study of pancreatic and gall bladder functions by means of secretin in 9 patients with peptic ulcer and 7 patients with non-specific ulcerative colitis. The findings in these patients are evaluated by comparison with the results of similar studies carried out on 22 healthy subjects.

A deficiency in pancreatic secretion has been suggested as a factor in the etiology of peptic ulcer. In the ulcer patient the duodenal pH is lower than in normal subjects (1) possibly because neutralization of the acid gastric contents in the duodenum is not as efficient as in the non-ulcer subject (2). It has been suggested that in the patient with peptic ulcer the pancreas either may not be adequately excited to secrete sufficient bicarbonate fluid or else it fails to secrete even though the stimulus is adequate. Myers et al (3) have reported a measurable degree of pancreatic insufficiency in the ulcer patient but Comfort and Osterberg (4) could not find any significant differences in the pancreatic response to secretin between healthy subjects and peptic ulcer patients.

Recently Portis and Necheles (5) suggested that in idiopathic ulcerative colitis the ulcerations and infections may be due to the irritant action of active trypsin brought to the colon by the increased motility of the small intestine. By perfusing solutions of trypsin through the colon of anesthetized dogs they were able to produce acute ulcerative lesions of the colonic mucosa. However they were unable to demonstrate higher trypsin activity in the colostomy drainage fluids of patients with ulcerative colitis than in patients with cancer of the colon. In more than one hundred dogs subjected by Saltzstein and coworkers (6) to the Mann-Williamson operation of draining the pancreatic juice and succus entericus into the terminal ileum ulcerations of the colon were not observed even in animals surviving three months. Ivy (7), in chronic experiments on dogs, found no ulcerative lesions of the colon when the pancreatic secretion was short-circuited directly into the colon.

Since the trypsin implicated in the theory of Portis and Necheles is of pancreatic origin, we thought it of interest to determine whether in patients with idiopathic ulcerative colitis the fasting as well as the secretin-stimulated pancreatic secretion contains abnormally high concentrations of trypsin.

In the course of a comparative study of the cholecystogram and the secretin test, Snape, Friedman and Swenson (8) made the incidental observation that many subjects with non-specific ulcerative colitis showed a non-functioning gall bladder. The present study was therefore extended to include determinations of gall bladder function by means of the secretin test. The rationale of this procedure, described first by

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Department of Physiology, The Jefferson Medical College, Philadelphia, Pa.

Lagerlöf (9) and subsequently by Diamond and Segal (10), is briefly as follows. In addition to stimulating the pancreas, secretin stimulates the liver to secrete bile. Normally most of the secretin-stimulated liver bile is taken up by the gall bladder so that the duodenal contents only occasionally contain traces of bile. In the cholecystectomy patient and the patient with a non-functioning gall bladder the hepatic bile enters the intestine directly (8, 11). Hence measuring the bile pigment concentration of the duodenal contents aspirated after secretin injection offers a test for the capacity of the gall bladder to concentrate bile. The secretin test for gall bladder function has been found to correlate well with both clinical findings and the cholecystogram (8).

## METHODS

The procedures employed in the present study have been described elsewhere (9, 10, 8). Gastric and duodenal contents were collected by continuous aspiration, using a Lagerlöf type biluminal tube. Exact position of the tube in the small intestine was checked by fluoroscopy. Following collection of the fasting contents for 20 or 30 minutes, secretin (1.1 clinical units per kilogram body weight) was given intravenously and collections continued for another sixty minutes. The secretin used in these studies was obtained from Wyeth, Inc. It had been prepared by the method of Friedman and Thomas (12); it was free from chologeic and pancreozymin-like effects and did not excite intestinal secretion.

Bicarbonate determinations were made by the titrimetric method of Van Slyke (13), and lipolytic activity was determined on a tributyrin substrate (14). The picric acid method of Myers, Free and Rosinski (15) was used to estimate amylase concentrations. The trypsin concentration was determined by the photo-turbidometric method of Riggs and Stadie (16) as modified in this laboratory (17). Bilirubin concentrations in the duodenal samples were determined by the method of Malloy and Evelyn (18).

## RESULTS

*Pancreatic Secretion.* The data for the fasting and secretin-stimulated pancreatic secretion in patients with peptic ulcer, non-specific ulcerative colitis, and normal subjects are summarized in Table I. In all three subjects the secretory response of the pancreas to injection of secretin was essentially similar. In both the peptic ulcer and the colitis patients the total volume of juice secreted per hour, as well as the total hourly output of bicarbonate and enzyme were within the range of values obtained in normal subjects.

*Gall Bladder.* In one of the nine peptic ulcer patients the gall bladder had been removed several years previously; the typical cholecystectomy bile pigment curve was found in the duodenal content following secretin injection. In the other eight peptic ulcer patients the pigment curve was similar to that of the normal series

TABLE I  
Pancreatic secretion in response to secretin.

Subjects	Fasting				Secretin					
	cc/20min.		Trypsin K x 10 <sup>-3</sup>	cc/hr.	HCO <sub>3</sub>	Trypsin K x 10 <sup>-3</sup>				
	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.		
Normal, 22 cases	1	52	10	300	82	283	63	123	56	434
Peptic ulcer 9 cases	14	58	0	212	93	240	59	123	112	280
Ulcerative colitis 7 cases	6	19	10	230	112	297	71	140	100	312

and it was concluded that gall bladder functions in these were normal. In view of the findings among patients with ulcerative colitis and constiveness (see below), it should be noted that several of the ulcer patients at times complained of "constipation."

Of the seven patients with non-specific ulcerative colitis the secretin test showed a non-functioning gall bladder in 4 patients. However, cholecystographic examination showed the gall bladder to be non-functioning in only one of these four patients. It is interesting to note that at the time the secretin study was made each of these four patients presented evidence of constiveness, while the remaining three patients had moderate or marked diarrhea.

#### DISCUSSION

In patients with peptic ulcer the pancreatic response to secretin administration was found to be essentially normal. This leaves open the question whether in these patients the pancreatic secretion in response to food substances is also normal. Pancreatic secretion in response to food in the intestine is probably excited by both the secretin mechanism and entero-pancreatic reflexes. Failure in elaboration of endogenous secretin or inadequate reflex excitation of the pancreas, or both, may occur even though the response to exogenous secretin is normal. We believe that this aspect of the ulcer problem warrants further investigation.

No evidence was obtained that the pancreatic secretion in patients with non-specific ulcerative colitis has abnormal concentrations of trypic enzymes. Even if hypermotility of the bowel should bring high concentrations of proteolytic enzymes to the colon, it is questionable whether this alone would be responsible for ulcerative lesions of the colonic mucosa. In diarrheal states other than colitis, hypermotility may be present but no ulcerations occur. However, it is possible that under certain conditions of disease the colonic mucosa might be susceptible to proteolytic digestion.

Gall bladder function was found by the secretin test to be normal in the patients with peptic ulcer but abnormal in more than half of the patients with colitis. This dysfunction occurred apparently only in those patients who had a tendency towards constipation even though they had all clinical and laboratory evidence of non-specific ulcerative colitis. Whether a

similar high incidence of non-functioning gall bladder occurs in individuals who are constipated but do not have colitis is at present being determined. Numerous viscero-visceral reflexes involving the gall bladder have been described. Gall bladder functions may be influenced by reflexes from the lower bowel, such as those initiated by bowel distension with fecal masses. The experiments of Youmans and Meek (19), Patterson et al (20), and others on dogs, showing the inhibitory effects of rectal distension on various visceral functions would support this view. In addition, one should also consider whether inflammatory processes in the ulcerated bowel do not make the bowel mucosa more sensitive and lower the threshold for reflex stimuli.

#### SUMMARY

Pancreatic and gall bladder functions by means of secretin were studied in 9 patients with peptic ulcer and 7 patients with non-specific ulcerative colitis. In the peptic ulcer patients both pancreatic and gall bladder functions were essentially normal. In the patients with colitis the secretion of proteolytic enzymes by the pancreas was within normal range but a non-functioning gall bladder was found in 4 of the 7 cases. The significance of these findings in relation to the etiology of the diseases is discussed.

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## THE CLINICAL AND ROENTGENOLOGICAL FINDINGS IN STEATORRHEA OF VARYING ETIOLOGY

CHR. JUEL BJEKELUND AND OLE W. HUSEBYE, Oslo, Norway

We desire particularly to compare the roentgenological, clinical and, where possible, the pathologic-anatomic findings in steatorrhea of different etiologies. We have tried to distinguish between the x-ray signs due to organic changes and those due to functional disturbances. We tried to determine if the roentgenological signs, such as the "moulage sign" and the "flocculation of the opaque meal" were due only to the increased fat content of the intestine. In other words do these signs, which usually appear in idiopathic steatorrhea, also occur in all other types of steatorrhea?

According to Hess Thaysen, fatty stools were first described by Kuntzmann in 1820 in pancreatic disease. A more elaborate description of pancreatic steatorrhea was made by Bright in 1833. In 1855, Gull described fatty stools in patients with mesenteric gland disease and he segregated these from pancreatic steatorrhea. Although tropical sprue had long been well known in tropical and subtropical regions, Manson's report in 1880 really made it a clinical entity. In 1888 Gee described the "celiac affection" (celiac syndrome) in children between 1 and 5 years of age, characterized by fatty stools, weight loss, pot belly, anemia and psychic disturbances. Idiopathic steatorrhea ("non-tropical sprue") became well known through the classical monograph of Hess Thaysen in 1932. The term "symptomatic sprue" has more recently been used where extensive intestinal or mesenteric disease has caused decreased fat absorption. Salvesen and Kobro, among others, have given detailed descriptions of such cases.

Among adults in non-tropical countries, three main types of steatorrhea occur (1) pancreatogenic steatorrhea, (2) symptomatic sprue (3) idiopathic steatorrhea or non-tropical sprue.

*Pancreatogenic steatorrhea* may be found in a number of diseases of the pancreas, particularly pancreatic fibrosis and atrophy, pancreatic lithiasis and calcification, as well as tumors and cysts of the pancreas. Characteristic signs arise from the external as well as the internal dysfunction of the gland. Reduction in the external secretion may be disclosed by examining the duodenal juice, or more easily through clinical and laboratory evidence of faulty fat and protein digestion. Lack of lipase causes steatorrhea, while lack of trypsin causes creatorrhea and azotorrhea. Microscopic stool

examination, while on Schmidt's diet, shows undigested muscle fibers, and chemical examination of the feces reveals increased nitrogen content, above 3 gms. per day. While these are important for the diagnosis, the lack of amylase is of minor diagnostic interest. Hypoinsulinism, due to the destruction of the islets of Langerhans, may produce hyperglycemia, glycosuria, a diabetic type of glucose tolerance curve and even serious diabetes. Jaundice may result from involvement of the bile ducts. Atrophic glossitis, aphthous stomatitis, macrocytic anemia and the B-avitaminotic symptoms commonly seen in idiopathic steatorrhea seldom are seen, although they have been described (Francisco). Thus pancreatic steatorrhea usually may be distinguished from the other types of steatorrhea.

*Symptomatic sprue* may be observed in Hodgkin's disease, lymphosarcoma and reticulosarcoma in the small bowel and the mesentery, in chylangioma of the mesentery, in tuberculosis of the mesenteric glands, in tuberculous enterocolitis and in nonspecific regional enteritis and enterocolitis, in gastrointestinal fistulae, in strictures of the gut and following small bowel resections. Destruction of the intestinal wall and blockage of the mesenteric lymphatics are assumed to be the cause of the faulty fat absorption. The clinical picture may rather closely resemble that of idiopathic steatorrhea but the course of the disease will often be more rapid and malignant because of the serious local disturbances.

*Idiopathic steatorrhea*,—non-tropical sprue—is chiefly noted for its manifold and varied symptomatology. Disturbances of metabolism, vitamin deficiencies as well as endocrine and hematological disorders play an important rôle. Asthenia, weight loss and abdominal symptoms are general features but the following are of diagnostic importance,—steatorrhea without simultaneous creatorrhea and azotorrhea, a flat glucose tolerance curve, osteoporosis, hypocalcemia (not infrequently with tetany), hypoproteinemia with edema, anemia, atrophic glossitis and stomatitis. The anemia may be microcytic (hypochromic) or macrocytic (hyperchromic), sometimes with a transition from the first to the second type during the illness. However all these signs are not always present and there may be considerable variation in the clinical picture.

It is often extremely difficult to distinguish between symptomatic sprue and idiopathic steatorrhea and sometimes the diagnosis is made at post-mortem. Symptomatic sprue is usually caused by changes in the intestine and the mesentery and x-ray examination of the

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digestive tract will frequently disclose these changes, as well as their location. Forsell's basic work on mucosal patterns as related to intestinal function showed that the circular folding is the resting relief of the mucous membrane and helps us judge the autoplacticity of the membrane. The following x-ray signs have been emphasized by various authors as important in idiopathic steatorrhea, — (1) Dystonia, i.e., variable caliber of the lumen (2) Loss of variability in the mucosal pattern, a sign of decreased autoplacticity, until eventually only circular folds are seen. (3) Sausage-like masses of barium in the intestine (the moulage sign) and flocculation of the opaque meal, so that no mucous membrane relief can be seen.

When this third sign is present, we cannot be sure that the contrast medium has conformed to the outline of the mucosa or whether the medium itself has merely been molded by the influence of the intestinal juice. The rate of transit may vary also, so that it may be either too short or too long.

#### INVESTIGATION

The material consists of 12 selected cases of steatorrhea, studied and treated from 1936 to 1948 in the medical department of the University of Oslo, as follows:—2 cases of pancreatic steatorrhea, one of which was operated upon; 4 cases of symptomatic sprue verified either at operation or post-mortem; 6 cases of idiopathic steatorrhea in 5 of which diagnosis was based upon clinical findings and x-ray studies and 1 upon post-mortem examination.

*Method of x-ray examination.* One glass of barium mixture was consumed in small sips during a period of 30 minutes. The patient then is examined after  $\frac{1}{2}$ , 1, 2, 3, 4,  $\frac{1}{2}$ , 8 and 24 hours, films being taken when necessary. The pathological investigations were made in the pathological laboratory under Professor Leiv Kreyberg, M. D.

In all cases the cardinal symptom was steatorrhea. Periodically the fecal volume was increased. The fecal color was light, glossy, greyish white with the usual consistency of porridge but sometimes fluid, as in cases V, VII, VIII, X and XI. The others had no diarrhea. Microscopic examination of the stools with Sudan III always showed considerable amounts of fat. Undigested muscle fibers were seen in the stools of the 2 patients with pancreatic steatorrhea but not in others except when diarrhea was present. Ewald's test meal showed achylia in cases I, VII and VIII, as well as in case IV during the last two periods. The others had normal acidity. The leukocyte count was in all cases normal or subnormal except for transient increases due to intercurrent infections. Except in case No. II, the icteric index was normal. In case No. II the pancreatic disease caused a partial occlusion of the bile ducts. Variations in the sedimentation rate were of no diagnostic value. Table 1 and 2 present a survey of the material and the most characteristic laboratory findings.

#### CASE REPORTS

*Case 1, hospitalized Apr. 7 to Dec. 11, 1943.* A 57 year old man during the years 1929 to 1932 had numerous attacks of severe upper abdominal pain associated with gastric upset, and since the Spring of 1940 constant steatorrhea associated with achylia. Radiological examination of the gall bladder, stomach and duodenum were negative. During the autumn of 1942 he showed increasing general edema, paresthesias of the legs, moderate hypochromic anemia and dyspnea and weakness on exertion. He was pale, weak and emaciated with massive edema, and a swollen and insensitive abdomen with signs of peritonitis. He was found to have a histamine-fast and constant achylia. The duodenal juice contained bile but no trypsin, lipase or amylase. The barium meal appeared after  $4\frac{1}{2}$  hours in the lower part of the ileum. (Figs. 1a and 1b). After 8 hours some of the barium meal had arrived in the cecum, the transit rate being therefore slower than usual. The loops of the upper jejunum are dystonic, wide and relaxed, and disposed in large curves. There is a predominantly circular folding of the mucosa but the membrane re-

TABLE I

Case no.	Diagnosis	Sex	Age	Average weight of feces p.d. gm.	Benzidine reaction	Faeces analysis (Schmidt diet)				Gluc. tolerance test (50 gm per os)		
						Fat in % of dry s.	Neutral fat in % of total	Excreted fat p.d. gm.	Excreted N p.d. gm.	Fasting bl. sug. mg %	Max. bl. sug. mg %	Max. rise mg %
1	Pancreat. steatorrhea	M	57	570	—	51	22	109	12.6	85	210	125
2	Pancreat. steatorrhea	F	48	920	—	56	10	68	7.3	165	345	180
3	Reticulosarcoma in the intest. and the mesent.	M	55	640	+					90	157	67
4	Hodgkin's disease	M	44	570	+	39	16	36	3.5	104	123	19
5	Chronic enteritis with lymphadenitis	M	43	950	—	59	17	104	3.9	92	117	25
6	Regional jejunitis with lymphadenitis	F	54	540	+	54	17	21	1.5	105	129	24
7	Idiopat. steatorrhea	F	59	930	—	57	13	39	3.3	93	133	40
8	Idiopat. steatorrhea	F	36	280	—	55	14	50		102	117	15
9	Idiopat. steatorrhea	F	36	610	—	46	7	28	2.3	94	99	5
10	Idiopat. steatorrhea	M	58	740	—	62	17	96	5.9	100	115	15
11	Idiopat. steatorrhea	M	48	390	—	50	6	36	0.4	88	108	20
12	Idiopat. steatorrhea	M	34	490	—	54	19	37	2.6	92	142	50

TABLE II  
Serum protein

Case no.	Hgb.	R. B. C.	M.	C.	H.	Serum iron	Serum protein				Phosphatase (alc.) Bodan. un.
							Total	Alb.	Glob.	N. P. N.	
gm	mill	gm x 10	%	%	%	%	mg%	mg%	mg%	mg%	
1	11.0	3.32	33	4.44	1.75	2.69	19.1	7.65	3.85	14.5	
2	11.3	3.36	34	5.82	3.47	2.35	26.9	8.00	2.80	69.5	
3	12.7	4.56	28	3.41	1.85	1.56	23.9	9.23	3.63	6.0	
4	9.9	3.14	32	5.6	4.62	2.45	2.17	16.9	7.90	2.85	3.4
5	10.8	3.78	28	4.92	1.39	3.53	29.1	7.60	3.10	3.5	
6	9.1	1.88	48	5.9	3.07	1.73	1.34	20.5	6.85	3.60	4.4
7	8.3	4.02	21	3.91	1.54	2.37	23.4	7.53	1.18	8.7	
8	10.2	3.85	27	4.34	2.54	1.80	15.1	8.93	3.33		
9	8.6	2.13	40	128					9.00	3.00	3.9
10	11.2	2.92	38	132	6.20	3.54	2.66	23.4	8.99	3.10	6.4
11	11.6	2.69	43	96	7.03	4.00	3.03	17.0	8.00	3.30	2.7
12	11.7	4.43	26	6.74	4.39	2.35	28.2	9.75	3.60	4.0	



Fig. 1. Patient no. I. Pancreatogenous steatorrhea. A somewhat decreased rate of transit. Dilated relaxed jejunal loops, mostly with circular folds. Some variation of the pattern of the mucous membrane. No typical moulage signs.

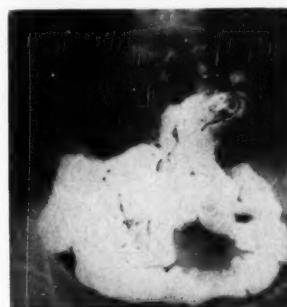


Fig. 2. Patient no. II. Pancreatogenous steatorrhea. Normal rate of transit. Wide, relaxed loops with mostly circular folding in jejunum. More varied pattern in the ileum. No typical moulage signs.

## STEATORRHEA

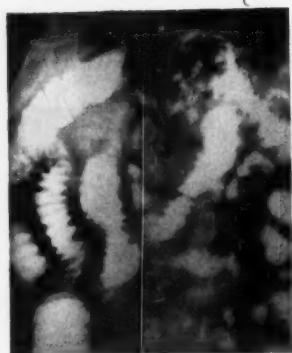
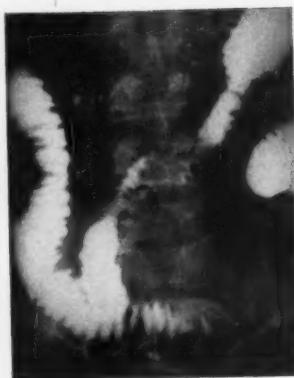


Fig. 3. Patient no. III. Reticulosarcoma in the small intestine and the mesentery. Decreased rate of transit. Wide jejunal loops, mostly with regular, circular folds. Infiltration in the middle part of the jejunum.

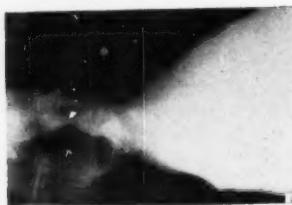


Fig. 4a and b. Patient no. IV. Hodgkin's disease. Definite moulage signs and flocculation of the contrast. Lack of mucous membrane pattern with signs of dystonia of the intestine, resembling a case of idiopathic steatorrhea.

Fig. 4c. Patient no. IV. Hodgkin's disease. Demonstrates a special picture of the stomach, with rigid unchanged contours, slightly jagged, but without any tumor-defects.



Fig. 5. Patient no. V. Chronic enteritis and regional adenitis in the mesenteric glands. Possibly a somewhat increased rate of transit. The small intestine relaxed and dystonic. Some fluid levels are observed. Slight moulage signs particularly in the ileum. The jejunal mucous membrane pattern is less varied than usual.



6a



6b



6c



6d

Fig. 6a, b and c (supine position and erect position). Patient no. VI. Regional jejunitis. Sept. 20th, 1947. The upper part of the jejunum is dilated. The loops below are constricted. The contours are irregular and the mucous membrane pattern shows coarse irregular folds of a considerable part of the jejunum. Normal rate of transit. The roentgen findings resemble those of an acute or more subacute jejunitis. The loops are stereotypic from film to film.



7a



7b



7c



7d

Fig. 7a and b. Patient no. VIII. Idiopathic steatorrhea 1940. A somewhat decreased rate of transit. The jejunal loops are wide and relaxed, and the variation of the mucous membrane pattern is reduced with mostly circular folds. A few fluid levels in the jejunum.



Fig. 8. Patient no. IX. Idiopathic steatorrhea. Normal rate of transit. The jejunal loops are wide with several fluid levels. Dystonia. Mouillage sign.



Fig. 9. Patient no. X. Idiopathic steatorrhea. Normal rate of transit. Wide relaxed intestinal loops. Dystonia. Possibly presence of mouillage signs.



Fig. 10a. Patient no. XI. Idiopathic steatorrhea. (May 1947) Increased rate of transit. In the upper part of the small intestine the loops are wide, dystonic, with regular circular folds. Flocculation of the opaque meal.

Fig. 10b. Patient no XI. Control (Nov. 1948). Still increased rate of transit. No definite dystonia.

lief has a fairly normal, distinct pattern. Flocculation (the moulage sign) is absent. During treatment with low fat diet and pancreatic, the fat and nitrogen content of the feces decreased, with a simultaneous increase of urinary nitrogen, indicating an increased nitrogen metabolism. The serum protein increased to the normal values, the edema disappeared and the polyneuritis receded. The weight increased from 50.6 to 61.8 kilos. His anemia did not respond to liver therapy but the blood values slowly increased without special treatment, and he was discharged from the hospital in good health.

*Case 2, hospitalized June 6 to Oct. 4, 1947.* A 48 year old woman in whom conservative treatment failed to control gastric pain, distention, jaundice and hepatic enlargement, was subjected to cholecystostomy at which operation the head of the pancreas was found enlarged and infiltrated with simultaneous enlargement of the liver and distention of the gall bladder and common bile duct. Following operation, the abdomen swelled and 2 weeks later a large tumor was observed in the position of the pancreas. Re-operation on Feb. 25, '46 revealed a cyst in the head of the pancreas, which was anastomosed with the stomach. From August onward she developed more gastric pain, distention, slight jaundice and itching of the skin. By January 1947 she had constant steatorrhea and somewhat later developed abnormal thirst and glycosuria.

She was now weak, exhausted, emaciated, with low blood pressure. The liver and spleen were not palpable, the abdomen thin, soft, slightly tender. The uterus index was increased slightly (7 to 12) with periodic increases to 25; the prothrombin index was 70, and she now had diabetes. The barium meal is observed in the lower loops of the ileum after 4½ hours, and after 8 hours entirely in the ascending colon. (Figs. 2a and 2b). The loops of the jejunum are wide and relaxed, mostly with regular circular folds of the mucosa and rather small variations in the pattern, while in the ileum the pattern is nearly normal, no moulage signs being observed. Her anemia disappeared as a result of treatment with iron. The diabetes proved difficult to regulate with insulin, so that the blood sugar values varied a great deal. She showed constant massive steatorrhea and weakness and after her discharge she showed gradual deterioration and died 3 months later in another hospital. No post-mortem examination was done.

*Case 3, hospitalized Nov. 15, 1945 to Jan. 2, 1944.* A 55 year old man for 3 months prior to admission experienced gastric pain, distention, anorexia, and great weakness with ultimate development of massive edema in the serotum and lower extremities. In spite of anasarca and bilateral pleural transudate he lost 5 kilograms weight while in the hospital and showed a large distended abdomen. A scant film of the abdomen in the supine position showed separation of the intestinal loops as a sign of fluid in the peritoneal cavity but there was no evidence of intestinal obstruction. The opaque meal passed the small intestine in the usual time. After 3 hours however (Figs. 3a, 3b, and 3c) one can recognize a shrinking process in the jejunum projecting itself over the 4th lumbar vertebra, and in the erect position a fluid level is observed. At this place the barium is in the lower part of the ileum and after 5 hours in the cecum. After 8 hours a considerable amount of barium is seen in the ascending colon but there still is a generous amount in the small bowel. After 24 hours all barium has passed into the colon. Thus the rate of transit is seen to be fairly slow. The loops of the small intestine, particularly the jejunum, are tremendously distended. The mucous membrane shows fairly regular and circular folds, but in some places a more normal autoplasticity is noticed. The caliber varies somewhat in different parts of the intestine.

At first subfebrile, later febrile with temperatures between 37.5 and 38.8° (C), the patient's condition deteriorated with anorexia, weight loss and increasing edema. He died marasmic. Autopsy revealed reticulosarcoma localized to the small intestine, the mesenteric glands and the retroperitoneal glands. The upper part of the small intestine was markedly distended. The lower part was bent at a sharp angle because of a string like adhesion to the right iliac fossa, but this adhesion left no mark of constriction. Throughout the whole length of the small intestine were found numerous nodes ranging in size from peas to marbles, partly flat, partly rounded and yellow-white on section. The mucous membrane was normal except for many dot-like hemorrhages. The mesentery was thickened and had several nut-sized nodes, likewise yellowish white on

section, and the same changes were found in the retroperitoneal glands. Histologically, these nodes were malignant and were diagnosed, *reticulosarcoma*.

*Case 4, hospitalized at various times in 1947 and 1948.* In 1946, a 44 year old man complained of epigastric pain after meals and periodically had aphthous stomatitis and sore tongue, and in 1947 developed a constant steatorrhea with weight loss of 10 kilograms in 8 months. The moulage sign was present. On low fat diet and folic acid he improved but still retained the steatorrhea. On readmission, he had become worse, and achylia was present. An abnormal x-ray picture of the stomach led to laparotomy, at which the root of the mesentery was found edematous and thickened with numerous bean-sized, firm, adherent glands. In spite of treatment with penicillin, Doca and x-ray he soon died. In spite of blood transfusions he had developed a progressive macrocytic anemia, hypocalcemia and hypoproteinemia. At autopsy, Hodgkin's Disease was found, localized to the stomach, small intestine and the mesenteric glands and adrenals. The distal end of the stomach was diffusely infiltrated with an ulcerating tumor like swelling on the posterior wall. In the small intestine a more diffuse and partly ulcerating infiltration was found particularly along the mesenteric border. The mesentery contained firm, infiltrating lymph glands up to the size of hazel nuts, with surrounding edema. A massive infiltration was found in the adrenals, which together weighed 35 gms. This adrenal involvement explained a low blood pressure and low serum chloride values found during the last weeks of his illness. The histological diagnosis was *Hodgkin's Disease*.

*Case 5, hospitalized Aug. 31, 1946 to Aug. 29, 1947.* The pre-admission history of this 43 year old man showed gastric distress after meals, weight loss, diarrhea, and steatorrhea at times, complicated by a hypoprothrombinemia manifesting itself by hematuria, mucosal bleeding, skin ecchymoses and responding promptly to the administration of vit. K. On admission he was pale, weak, with considerable edema of the legs, and a weight loss of about 9 kilograms. X-ray studies showed some intestinal hypermotility, while the loops of small bowel were dystonic with flocculation of the barium and the mucosal pattern was somewhat rigid. His general condition did not improve on vitamins and plasma transfusions and his anemia which was nonresponsive to folic acid improved with iron medication. He had some attacks of tetany. Signs of peritonitis led to an operation, at which free air was noted in the cavity, and an unexplained rupture 10 cms. long in the anterior surface of the cecum with protruding, dirty gray mucous membrane covered with fibrin.

The small intestines were injected and edematous with thickened walls throughout, especially distally.

The root of the mesentery showed increased thickness and edema and there was a series of firm and greatly enlarged lymph glands, some of which were as large as hen's eggs. Complete anuria set in and he died in a few days of uremia. No autopsy was done.

*Case 6, hospitalized from Sept. 1947 to October 1948 at intervals.* A 54 year old woman complained of stinging abdominal pain, distention, nausea, vomiting and a loss of 8 kilograms in 2 months, during which time edema developed in the legs. Examination showed pallor, weakness and anasarca, B. P. 80/50, abdominal tenderness on the left side and some ascites. The stool culture for T. B. was negative. Barium series showed normal intestinal motility with slight retention in some of the jejunal loops. The upper part of the jejunum is distended, and below this the gut is markedly constricted and the mucosal folds are coarse, irregular and show stereotyped contours. (Figs. 6a and 6b supine; 6c, erect). A diagnosis of jejunitis was made; and later x-ray examinations confirmed this. The general condition deteriorated in the first 4 months, with marked weight loss, the abdomen showing a palpable mass to the left and above the umbilicus. Usual forms of treatment did no good and, since it was suspected that a local process in the small gut might be the cause of the steatorrhea, the abdomen was opened on Jan. 21st. The jejunum for a distance of ½ of a meter was found swollen and edematous throughout the whole of its circumference, but especially along the mesenteric edge. The mesentery likewise was thickened and edematous particularly toward the root, which presented a large tumor-like swelling and prominent masses the size of hen's eggs, while the serosa of the mesentery was very hyperemic. Histological examination of a lymph node showed leukocytic infiltration and many plasma cells with some mast cells and eosinophils, but there were no signs of malignancy, tumor cells or giant cells. The histologi-

cal diagnosis was *lymph nodes with chronic inflammation*. In March 1948 deep x-ray therapy (total, 1400 r units) was applied to the abdomen, and beginning in June the condition improved, with disappearance of dyspepsia, and a weight gain of 10 kilograms in 2 months. The serum calcium and serum protein values increased slowly to normal during the next few months and the edema and ascites disappeared. X-ray examination, Aug. 18, 1948, showed that the mucosa now had a regular pattern and the single folds were clearly seen. The former constriction and rigidity of the intestine had now almost disappeared. The loops lay in fairly large curves, possibly owing to adhesions, and only in one place there was a constricted area about 4 cms. in length.

The blood studies on this patient were interesting. On admission her blood picture was normal, but during the first 6 months she developed a macrocytic anemia with a megaloblastic bone marrow and leukopenia (2000 to 4000). This anemia was only partly helped by blood transfusions but later responded perfectly to folic acid and in 2 months reached normal values, with disappearance of the abnormal bone marrow smear picture. She made a good recovery and returned to work, although the feces still contained increased fat. A final x-ray check-up showed some hypermotility (Fig. 6d.). The diseased loops of gut lay as before, fairly adherent, but the contours were soft and even, and the mucosal pattern was normal.

**Case 7, hospitalized Sept. 19, 1935 to Jan. 21, 1936.** A 59 year old woman had had a resection of the stomach because of invertebrate dyspepsia but the specimen showed only atrophic gastritis. Her usual symptoms persisted—pain, vomiting, diarrhea, anorexia, weight loss, weakness, glossitis and finally she developed edema and ascites. The blood pressure usually was low, e. g., 85/55. Blood smear showed anisocytosis and some polychromasia and a shift to the left in the differential count. X-ray examination showed the absence of the stomach. The barium was all in the colon in 3 1/2 hours, with small quantities still left in the small bowel. The upper jejunal loops showed a fairly irregular caliber and the mucosal pattern was circular and stereotyped, and some flocculation was noted. X-ray examination of the bones showed osteoporosis and osteomalacia in the spine. Treatment had no effect, necrotic sores appeared in the skin, the edema increased, and she died marasmic. Autopsy did not show anything of interest except mild inflammatory changes in the mucosa of the gut. Pathological diagnosis,—osteoporosis, bronchopneumonia.

**Case 8, hospitalized at various times between 1930 and 1948.** A 30 year old woman, since the age of 17, had shown periodically, anemia, gastric pains unrelated to meals, diarrhea, vomiting and steatorrhea. In 1940 she was emaciated and pale with some edema and a large soft belly without tenderness. The ascorbic acid and prothrombin levels in the serum were lowered. X-ray examination at that time showed a dystonic state of the small intestinal loops, (Figs. 7a and 7b) and the mucosal pattern was circular and poorly defined, with considerable flocculation of the barium. Although a number of fluid levels were seen in the jejunal loops, there was no indication of obstruction. Rest in bed, light diet, iron, HCl, and vitamins C and K increased the blood values to normal and there was slight improvement in the steatorrhea. In 1943 her blood was normal but steatorrhea persisted, though she was working as a farmer's wife. In November 1948, achylia was found, but the steatorrhea had disappeared and the serum proteins, serum calcium, serum phosphorus, serum phosphatase and the glucose tolerance tests all were normal. At this time the x-ray studies of the intestinal tract were normal (Figs. 7c and 7d.).

**Case 9, hospitalized at various times between 1940 and 1944.** A 36 year old woman, who for 14 years had had periodic steatorrhea, gastric pain, anorexia, weight loss, glossitis and aphthous stomatitis, developed diarrhea in 1940 with vomiting, some fever and hypochromic anemia (Hgb. 61 percent, R.B.C. 1,800,000) which did not respond to liver therapy. Blood smears showed up to 70 erythroblasts to 100 W. B. C. and numerous Howell Jolly bodies, while the bone marrow showed fairly vigorous erythropoiesis with megaloblasts and Howell-Jolly bodies. The serum ascorbic acid and prothrombin levels were somewhat reduced. An x-ray barium series showed the meal in the cecum after 4 hours and practically all of it in the colon after 8 hours. The jejunal loops are wider than normal where the barium appears in cascades and the moulage sign is present. She improved on rest and liver extract but in September developed pleurisy, the exudate giving a positive

culture for T. B. But she recovered and the steatorrhea decreased. Later on, she had periodical steatorrhea again with glossitis and stomatitis. Hypochromic anemia again appeared in 1942. In 1944 she had no anemia, moderate steatorrhea and a flat glucose tolerance curve. In 1945 she died in another hospital of miliary T. B. (Figs. 8a and 8b.).

**Case 10, hospitalized Oct. 31, to Dec. 7, 1946.** A man of 58 years of age, for the past 4 years has had periodical steatorrhea, diarrhea, weakness, weight loss and anemia but became worse in 1944 and his bone-marrow showed megaloblasts. The barium meal after 4 hours was in the lower part of the ileum and after 8 hours nearly all in the colon, though traces are observed in the small gut. (Fig. 9). A film at 9 hours showed distended loops of small intestine with regular and circular folds. No normal mucous membrane pattern is seen. The barium is seen clogging together everywhere and appears in irregular lumps (moulage sign). This picture resembles that seen in the celiac syndrome of children. No form of treatment improved the diarrhea or the steatorrhea and he failed to respond hematologically to folic acid. There was some improvement with blood transfusions but the patient went home against advice before treatment could be completed.

**Case 11, hospitalized several times in 1947 and 1948.** This man, aged 48, had for 20 years suffered from anemia, glossitis, aphthous stomatitis and fissures at the corners of the mouth, and had received treatment with iron and liver. For 10 years he had experienced pain in the left side of the abdomen with distention, and yellow stools like a baby, while more recently he had diarrhea with 6 or 7 loose, fat, glossy stools per day with weight loss and aggravation of his weakness and anorexia. The tongue showed papillary atrophy but no megaloblasts were found in the bone marrow. X-ray showed marked intestinal hypermotility and the loops of the small bowel, especially in the upper part of the belly, were wide and dystonic and showed circular folds. (Fig. 10a). Some flocculation of the barium appeared but further down the mucosal pattern was fairly good. Rest and treatment with folic acid improved him and the feces became firmer and the anemia disappeared. He went to work, still using folic acid and liver and further examination showed that the blood values, the sugar tolerance curve, the serum proteins and calcium remained within normal limits. Further x-ray studies showed a persistence of hypermotility but the dystonia was gone and the mucosal pattern normal. (Fig. 10b).

**Case 12, hospitalized Oct. 8 to Nov. 18, 1947.** For the past five years, this 34 year old man had had periodical dyspepsia responding to careful diet and x-ray studies had been negative. Six months prior to admission he began having loose, light colored, voluminous stools and glossitis and stomatitis, as well as weight loss. There was atrophy of the papillae along the edges of the tongue. The urine showed some albumin. X-ray studies indicated some intestinal hurry, as well as flocculation and moulage signs in the lower portion of the ileum. There was a fairly good mucosal pattern in the upper part of the small gut although the loops were wide and the folds abnormally coarse. The patient improved on simple rest and a light diet, and although the feces became less voluminous they were still decidedly fatty.

#### DISCUSSION

While the etiologies in these cases have varied, all have shown marked steatorrhea, and three main types of steatorrhea are to be noted.

**Idiopathic steatorrhea.** In our six cases of idiopathic steatorrhea,—as is always the case,—diagnosis can only be made by exclusion. While the examination of these cases revealed no definite condition which might produce steatorrhea, they all presented a varied assortment of symptoms which, as mentioned in the introduction, are characteristic of this disease. Autopsy verification was made only in Case VII but in the others continued observation supported the diagnosis, and the roentgenological examinations particularly showed changes which are in accord with the findings of others in idiopathic steatorrhea.

**Pancreaticogenic steatorrhea** can almost always be clinically segregated from the other forms. Our two

cases provided typical clinical pictures and in one of them the diagnosis was verified by an operation which disclosed a cyst of the pancreas. Roentgenologically, these two cases were also somewhat different from the idiopathic and symptomatic cases. (Compare Figs 1 and 2). X-rayed at a time when they were showing definite steatorrhea (68 and 109 gms. of fat per day, respectively) both showed relaxed jejunal loops, but very little change otherwise. The mucosal pattern was, in general, fairly normal, but in some places there were folds which were predominantly circular, and flocculation and the moulage sign seemed to be completely absent. (We have seen similar conditions in two children with steatorrhea caused by pancreatic fibrosis.) These x-ray findings may constitute a principle distinction between pancreatogenic and idiopathic steatorrhea, yet there is a chance that the findings were accidental. If they were *not* accidental, we may perhaps be permitted to conclude that the fat content in the intestine under these conditions cannot alone produce the moulage sign or flocculation of the barium.

*Symptomatic sprue.* In the remaining 4 cases, local causes of the steatorrhea were proved either at operation or autopsy. In case III reticulosarcoma was found in the small intestine, the mesenteric glands and retroperitoneal glands, and the course of the disease was rapid and malignant with marked hypoproteinemia. Radiographically, there were stasis, dystonia and alterations in the mucosal pattern but no moulage signs. (Fig. 3). Autopsy on case IV disclosed extensive Hodgkin's disease in the stomach, small intestine, mesenteric glands and the adrenals, the clinical picture bearing a striking resemblance to that of idiopathic steatorrhea. Serious gastric symptoms later developed with marked dysphagia, anorexia, vomiting and finally signs of adrenal insufficiency. The x-ray films resembled those of idiopathic steatorrhea but the stomach presented a bizarre infiltration of the antrum arousing suspicion of malignancy. (Fig. 4). In case V, during a whole year's observation, the diagnosis of idiopathic steatorrhea was never questioned, but operation revealed it to be a case of symptomatic sprue. The course of the disease was rapid and malignant and the small bowel showed edema with large glands in the mesentery, yet the x-ray films were not different from those obtained in the case of idiopathic steatorrhea seen in Fig. 5. Case VI was especially interesting because one could not make a clinical diagnosis from the abdominal distress, hypoproteinemia, edema and steatorrhea, yet the x-ray findings were diagnostically conclusive. There were regional changes in one part of the jejunum, (Fig. 6), and the loops of the intestine were constricted with irregular, stereotyped contours and coarse folds and were nearly immovable. Additionally there was barium retention in the diseased portion of gut, and the x-ray findings were interpreted as indicating regional jejunitis, due to infection or lymphogranulomatosis. The patient was operated upon because she was suspected of having malignant disease of the small bowel, but the histological diagnosis was merely, "chronic inflammation. She had the additional features of a macrocytic anemia with megaloblastic marrow all of which seemed to have been cured by x-ray therapy (see Fig. 6b).

#### CONCLUSION

In 2 of our cases of symptomatic sprue the x-ray examination of the small bowel rendered important

diagnostic information, but in the other 2 cases differentiation from idiopathic steatorrhea was not possible. In one of these, however, there were gastric changes indicating a local disease of the digestive tract. Our material furthermore shows that pancreatogenic steatorrhea differs from the other types not only clinically but radiographically. The scanty changes seen in the small bowel in these cases perhaps indicate that the fat content of the intestine cannot alone be responsible for the x-ray changes seen in the other types. It may be very difficult to differentiate between idiopathic steatorrhea and symptomatic sprue, but with better utilization of all diagnostic aids, some cases of the idiopathic syndrome may be recognized as symptomatic sprue. Repeated x-ray examination of the small intestine is of the greatest importance and should never be omitted. Yet sometimes the differentiation can be made only at operation or autopsy.

#### SUMMARY

In a survey of several conditions in which the common presenting sign was steatorrhea, clinical, pathological and radiographic studies suggested certain distinctions among the entities,—pancreatogenic steatorrhea, symptomatic sprue and idiopathic steatorrhea. The first of these differs clinically and roentgenographically from the two others. The moulage sign and flocculation of barium were not seen in our cases of pancreatogenic steatorrhea. In symptomatic sprue we have found that x-ray studies of the small intestine are of help in making the sometimes difficult distinction from the idiopathic syndrome. Above all, we found that repeated x-ray examinations of the small bowel are indispensable in all cases of steatorrhea, and we make a plea for its greater use in these cases.

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## AN APPROACH TO THE PROBLEM OF "EPINEPHRINE FASTNESS"

FREDRICK F. YONKMAN, M. D.\*; LEON LEVINSON, M. D.\*\* AND MAURICE S. SEGAL, M. D.\*\*\*

THERE have been several approaches to the problem of "epinephrine fastness," both as to its cause and its treatment. A recent rational addition is afforded by Cazort (1) and we should like to present still another which deals with the concept of histamine intoxication as one of the factors contributing to this condition. Three important experimental contributions form the background of our approach.

The first contribution is that of Hallion and Nepper (2) who, in 1911, observed that normal rabbits receiving lethal doses of epinephrine intravenously invariably died of marked pulmonary edema. The reason for the edema was not clear at that time.

The second contribution is that of Staub (3) who detected significant increments of plasma histamine, as well as whole blood histamine, in seven human subjects after each had received intravenously a therapeutic dose of epinephrine (0.2 mg.) (Fig. 1). Staub's work has been confirmed in animals by Farrerons-Co (4). Why histamine is released is a moot point but it seems rea-

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sonable that its hypotensive capacity might counteract, in a homeostatic effort, the hypertensive effects of epinephrine. It is evident from Fig. 2 that the plasma histamine reached its maximum soon after the highest elevation of systolic pressure had been produced by epinephrine. As epinephrine is oxidized, the return of blood pressure to normotensive levels is assisted by the action of histamine. Simultaneously, however, such released plasma histamine becomes available for its constricting effect on the sensitive bronchomusculature of the allergic patient whose asthma is being treated by epinephrine. Such constriction could be accompanied by further reduction in the size of the bronchiolar lumen because of edema, the production of which is one characteristic of histamine's manifold action (5).

The third contribution is that of Halpern and Cruaud (6) who stressed the significant fact that the marked pulmonary edema in rabbits following epinephrine intravenously, as described by Hallion and Nepper (2), could be prevented by an antihistaminic agent, 3272 R. P.

Correlation of these three significant studies leads one to the conclusion that failure of epinephrine to elicit duplicable and consistently favorable responses in the patient who becomes "epinephrine-fast" or "epinephrine-refractory" might be attributed to the histamine released with each subsequent injection of epinephrine. In terms of smooth muscle actions, that of histamine (contraction) might well predominate over that of epinephrine (relaxation) (Fig. 3), especially in view of

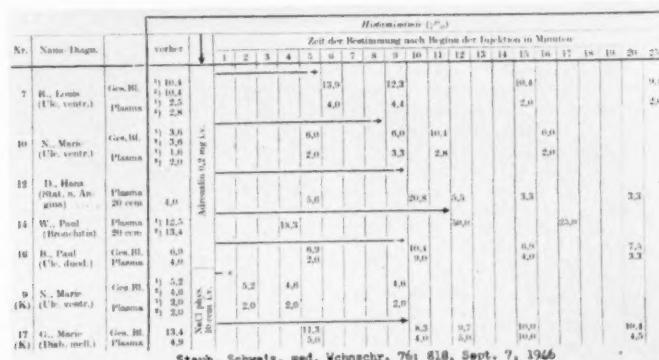


Fig. 1.

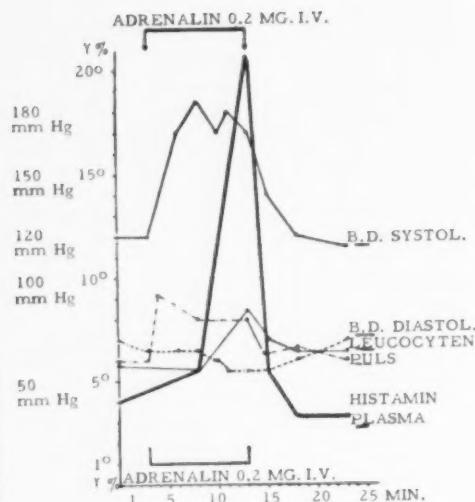


Abb. 1. D. H., Status nach Angina. V. 12. 29 J.  
Staub, Schweiz. med. Wochenschr. 76: 818, Sept. 7, 1946

Fig. 2.

the slower rate of degradation of histamine. Temporary relief would be possible but eventually a progressive encroachment of air passage would ensue. Although epinephrine is considered to be an antidiemetic agent, the more prolonged action of histamine would predominate over that of epinephrine, hence, the dual action of histamine (bronchoconstricting and edema-promoting\*) would eventually overrule those opposite actions of epinephrine, resulting in the condition known as "epinephrine-fastness" or more correctly, "epinephrine-histamine toxicity."

We have as yet not determined plasma levels of histamine; those should be determined and one might reasonably anticipate, from the valuable clinical results of antihistaminic therapy, a not inconsiderable plasma histamine concentration in the epinephrine refractory patient.

The use of an antihistaminic agent in the epinephrine-fast patient seems rational since the favorable actions of epinephrine would be permitted to exercise themselves unopposed by the antihistaminic agent even while this medicament exercised its specific antagonism toward the histamine released by the epinephrine. In fact, such favorable actions might well be enhanced in certain patients if "adrenergic potentiation" as pre-

\*Edema as a factor in impeding alveolar air transfer becomes more important in the light of the findings of Alley and Lindskog (Annals of Surgery, 128:497, 1948). These authors report marked edema of the interalveolar membrane following experimental lobar occlusion in the dog. Such edema could result in restriction of air transfer between alveoli (through the pores of Kohn) and thus further accentuate air hunger. If such pore occlusion prevailed in the atelectatic lung (or in the epinephrine fast asthmatic patient) such edema might play an important role since Alley and Lindskog have been able to prevent or diminish the extent of edema by appropriate antihistaminic agents.

viously described (7) should prevail under antihistaminic therapy. Preliminary evidence to substantiate these physiologic considerations was recently reported by one of us (M.S.S.) (8).

In a series of ten patients acutely ill in status asthmatics who were epinephrine-fast, we have employed intravenous tripeptenamine hydrochloride or diphenhydramine hydrochloride as a means for reestablishing epinephrine sensitivity. The injections were usually given at a rate of about 1 cc. (10 mg.) per minute either directly or through the tubing of intravenous infusions. Due to chemical incompatibility, such antihistaminic agents should not be mixed with solutions of aminophylline. The average dose was 30 to 50 mg. administered at intervals of four to eight hours over periods of one to four days. The dose was gradually reduced as the patient's condition improved until the drug was eventually discontinued. In eight of these ten patients significant improvement followed these procedures. Epinephrine, administered subcutaneously or by aerosol route, appeared to bring relief from acute paroxysmal bronchospasm, whereas previously only the side effects of epinephrine had been observed following its use.

A typical case history is that of L. K., a 55-year-old married female, who had been troubled with asthma for a period of four years. Until her present illness, the attacks had never been of any great severity and were generally relieved by subcutaneous administration of epinephrine. Repeated tests had been reported as negative. It was believed that emotional and psychic factors, as well as respiratory infections contributed greatly to her attacks.

In April of 1948 she developed a severe attack of asthma which necessitated hospitalization. She was treated with epinephrine, aminophylline by various routes, a variety of oral medications, numerous sedatives and oxygen. Despite the repeated use of aminophylline intermittently, she soon became refractory to most medications and presented a typical picture of status asthmaticus.

She was placed on an extensive program of continuous infusions of aminophylline in 5% glucose, meperidine, and aerosols of a bronchodilator spray. She made a splendid recovery and was home within ten days. After a period of complete well-being of over two weeks, she then had a relapse in which she again presented the typical picture of status asthmatics.

She was seen for a second time, approximately one month after the initial consultation, and at this time was refractory to continuous aminophylline intravenously, to sympathomimetic

#### INNERVATION OF BRONCHIOLE

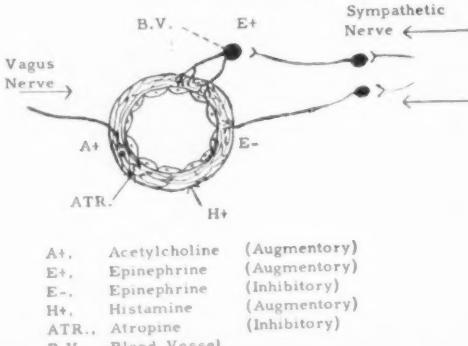


Fig. 3.

amines by various routes, to oxygen, and to sedation. She was started on a program of tripeleannamine intravenously, employing 50 mg. doses at four hour intervals. The solution was injected directly into the intravenous tubing continuing to supply the aminophylline-glucose infusion. Following the initial injection, bronchospasm was less marked and the patient became considerably relaxed and somewhat drowsy.

Approximately 20 minutes after receiving the initial dose of intravenous tripeleannamine, the patient was given 0.3 cc. of epinephrine 1:1000 subcutaneously. Following this, her wheezing became still less evident. Furthermore, she did not complain of the troublesome palpitation and headache that previously administered epinephrine had been producing. After a second injection of the antihistaminic agent, she once again gained considerable relief from her aerosols of one of the sympathomimetic amines with none of the side reactions previously observed. It was further noted that her response to aminophylline began to improve on this program, and the side effects from this preparation too, (jitteriness and nausea) were less evident.

Tripeleannamine was administered by vein in 50 mg. doses every four hours for the first day, and the dose was then gradually decreased. She continued to make excellent progress and after the fifth day all intravenous therapy was discontinued and she was placed on a program of rectal aminophylline, rectal tripeleannamine and aerosols of one of the sympathomimetic amines. She has remained symptom free on this program.

#### SUMMARY

1. A theoretical explanation for the epinephrine-fast state as a manifestation of imbalance in the histamine-sympathetic see-saw is presented ("epinephrine-histamine toxicity"). The experimental observations described lead us to conclude that repeated administrations of epinephrine to such individuals produce an increase in plasma histamine overcoming the effects of the epinephrine. It is theoretically plausible that suitably administered antihistaminic agents might return the see-saw to its normal balance.

2. In eight of a group of ten patients displaying epinephrine-fastness significant improvement followed the use of intravenous tripeleannamine hydrochloride or diphenhydramine hydrochloride. Epinephrine, administered subcutaneously or by the aerosol route, appeared to bring relief from acute paroxysmal bronchospasm, whereas previously only the side effects of epinephrine had been observed following its use.

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## COMPARATIVE CAPACITIES OF ADSORPTIVE AGENTS FOR ENDOGENOUSLY PRODUCED TOXIC CHEMICALS

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A CONCENTRATION of effort to control the external environment of the human body has led to a tendency to neglect the internal environment, and yet it is this internal environment, the gastrointestinal tract, to which the body is exposed 24 hours a day throughout life. The bacteria of the tract possess a capacity for synthesis of toxic chemicals from normal food elements; thus, histamine from histidine, tyramine from tyrosine, indole and skatole from tryptophane, etc. In addition to the known and harmful chemicals thus produced, there are doubtless a large number of toxic chemicals elaborated in small amounts in the gastro-intestinal tract which may far exceed the known members in their capacity to produce harmful effects. This sphere of investigation is vast and largely unexplored. The confining of these toxic agents to the gut lumen is an important, and definitely a long neglected phase of medicine. Adsorptive agents offer the logical solution. An adsorptive preparation capable of confining to the

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gut all toxic agents and yet permitting the absorption of vital food elements would be the goal.

It is to be borne in mind that each of the toxic chemicals produced endogenously has been associated with or implicated in clinical syndromes of various types. Infantile diarrhea of the proteolytic type is an excellent example. It is well-known that the small intestine is not well equipped to resist the passage of toxic products into the blood stream (2). In many cases of infantile diarrhea, a severe type of toxemia results, characterized by vomiting, diarrhea, emaciation and great prostration. In general, it can be said that if the normal defense mechanisms of the body are impaired the putrefactive products exert marked systemic effects.

One phase of the problem would be a study of the capacity of various adsorption agents for putrefactive chemicals. Martin and Wilkinson (1) reported the efficacy of a polyamine formaldehyde resin in adsorbing skatole and indole. Synthetic sodium aluminum silicate was found effective in adsorbing amines such as

putrescine, cadaverine, tyramine, histamine and guanidine. Kaolin was inactive as an adsorbing agent of histamine and skatole.

#### EXPERIMENTAL.

Thirty-five different materials were compared for their ability to adsorb skatole, indole, tyramine, putrescine dihydrochloride, histamine dihydrochloride and mercuric chloride in vitro. Solutions of the toxic agent (see table I) were prepared and to these solutions were added the various adsorbents at concentrations indicated in table I. The pH was adjusted with either sodium carbonate or hydrochloric acid. The mixtures were then shaken mechanically for one half hour and filtered. The filtrate was analyzed.

Indole was determined by reading the density of the solution in the Beckman Spectrophotometer at 268  $\mu$  and obtaining the concentration from the plot of Density versus Concentration. Indole obeys Beer's Law in the concentration range of 2.5 to 25 mg. per liter. A blank solution was prepared for each adsorbent.

Tyramine hydrochloride was also determined with the aid of the Beckman Spectrophotometer by reading its density at 276  $\mu$  and obtaining the concentration from the plot of Density versus Concentration. Tyramine hydrochloride obeys Beer's Law in the concentration range of 1 to 100 mg. per liter. A blank solution was prepared for each adsorbent.

Skatole was determined in the same manner at 280  $\mu$ . Skatole obeys Beer's Law in the concentration range of 1 to 25 mg. per liter.

Histamine dihydrochloride was determined colorimetrically with the aid of diazotized sulfanilic acid (3). The density of the color obtained was read at 500  $\mu$  and the concentration obtained from a standard curve. The color obtained obeys Beer's Law in the concentration range .01 to .05 mg. per cc.

Putrescine dihydrochloride was determined with the aid of the color reaction between amines and *B*-naphthoquinone-4-sulfonic acid (4,5). The red color obtained with putrescine dihydrochloride obeys Beer's Law in the concentration range 0.30 micrograms using a wave length of 500  $\mu$ .

Mercuric chloride was determined in the following manner:—10 cc. of each filtrate was placed in a 250 cc. beaker and diluted with about 25 cc. of distilled water. The solution was made alkaline with 40% sodium hydroxide, precipitating the mercury. The precipitate was allowed to stand for 5 minutes and then was filtered off onto a Gooch crucible using an asbestos mat. It was washed, dissolved in 3 cc. of concentrated nitric acid and washed into a 250 cc. Erlenmeyer with 50 cc. distilled water. 2 cc. of iron ammonium sulfate solution (8 gm./100cc.) was added as an indicator and the solution titrated with 0.1 N ammonium thiocyanate to an orange-brown end point. Each cc. of 0.1 N ammonium thiocyanate is equal to 10.03 mg. mercury.

The results obtained with the various materials tested are summarized in Table I.

#### DISCUSSION

Mutch (6) emphasized the differences in samples of kaolin. He reported that an English sample of kaolin adsorbed histamine, muscarine, solanine and other toxic agents with great efficiency. To eliminate the poten-

tialities of kaolin variations playing an important role, we obtained six different samples of kaolin and isolated the kaolin from one marketed preparation. The variation in the capacities of these seven different kaolin samples for histamine adsorption under the conditions of this study ranged from 18 to 42% averaging 29%. It is questioned therefore that major variations occur in kaolin samples, as obtained and marketed in the United States.

Charcoal has received the most concentrated study as an intestinal adsorbent. Joachimoglu (7) studying strychnine adsorption indicated an absence of correlation between *in vitro* and *in vivo* capacities. That this factor is of importance is obvious but Martin and Wilkinson (1) reported a positive correlation between the *in vitro* and *in vivo* adsorptive capacities of the polyamine resins and the sodium aluminum silicates. Variations in the adsorptive capacities of different charcoals was reported by Laquer and Sluyters (8). Results reported herein indicate very little difference among the three charcoals tested. It is probable that greater variations in manufacturing procedures existed some years ago and that today all activated charcoals are relatively constant in capacity for adsorption. Sjogren and Wallden (9) emphasized the difficulties involved in attempting to correlate adsorptive capacity of an adsorbing agent for one substance in terms of another. They pointed out that the adsorption of methylene blue could not be correlated with the capacity of charcoal to reduce the toxicity of mercuric chloride. Studies of the adsorption by charcoal of mercuric chloride, sulfanilamide, strychnine nitrate, morphine, atropine sulfate, nicotine, veronal, medinal, phenobarbital, sodium alurate, diaz, evipal, phanodorm, salicylic acid, phenol, alcohol and potassium cyanide were made by Anderson (10) who subsequently concluded that changes in pH which increase the dissociation of the substance to be adsorbed decrease its adsorption, and changes which decrease the dissociation increase the adsorption (11).

The selectivity of adsorbing agents is well illustrated by the effectiveness of polyamine resins in removing skatole, indole, mercuric chloride and histamine and yet being relatively ineffective against putrescine and tyramine. Again, the charcoals are extremely effective but fail to adsorb putrescine to any significant degree. Magnesium aluminum silicate is highly effective against putrescine and relatively ineffective against the other agents studied. Table I demonstrates the necessity of multiple adsorbing agents in adsorption therapy. The cation exchange resins despite their effectiveness could not be used in an intestinal adsorbent composition because these agents are known to remove minerals such as potassium, sodium, calcium, etc. Two other commonly employed intestinal adsorbents magnesium trisilicate and aluminum hydroxide, are relatively inefficient adsorption agents.

#### SUMMARY

35 different adsorbing agents have been studied for their capacity to adsorb toxic chemicals which in general are considered to be endogenously produced. The selectivity of adsorbing agents is of such a magnitude as to virtually dictate the employment of multiple adsorbing agents when they are employed therapeutically.

## COMPARATIVE ADSORPTION STUDY

TABLE I

ADSORBENT concentration—4gm./100cc except where indicated	SKATOLE % adsorp- tion—cone. 10 mg/100cc pH 8.0-8.5	INDOLE % adsorp- tion—cone. 50 mg/100 pH 8.0-8.5	TYRAMINE hydro- chloride—% cone, 100mg/ 100cc pH 8.0-8.5	PUTRESCINE dihydro- chloride—% cone, 150mg/ 100cc pH 8.0-8.5	HISTAMINE dihydro- chloride—% cone, 250 mg/100cc, pH 8.0-8.5	MERCURIC chloride % adsorption cone, 2gm/ 100cc, pH 1.5
1 Insoluble Polyamine anion Exchange Resin A, commercial sample 200 mesh.	96.0	96.0	24.5	36.7	60.0	97.7
2 Insoluble Polyamine anion Exchange Resin B, commercial sample 200 mesh chloride salt.	98.0	99.2	25.5	10.0	none	100.00
3 Insoluble Polyamine anion Exchange resin C, commercial sample 200 mesh.	97.0	95.6	20.5	none	none	8.0
4 Insoluble Polyamine anion Exchange Resin D, commercial sample 200 mesh.	92.0	77.5	16.5	none	28.0	73.0
5 Insoluble Polyamine anion Exchange Resin E, commercial sample 200 mesh.	64.0	58.0	11.0	10.0	24.0	100.0
6 Insoluble Polyamine anion Exchange Resin F, commercial sample 200 mesh.	53.6	47.0	10.0	8.0	72.0	100.0
7 Cation Exchange Resin A, Hydrogen Activated commercial sample 200 mesh	99.0	100.0	95.0	96.5	72.0	3.5
8 Cation Exchange Resin B, Hydrogen Activated commercial sample 200 mesh	98.0	100.0	99.5	96.2	98.0	13.0
9 Cation Exchange Resin C, Hydrogen Activated commercial sample 200 mesh	95.0	100.0	100.0	97.3	92.0	9.0
10 Cation Exchange Resin D, Hydrogen Activated commercial sample 200 mesh	98.5	100.0	96.5	94.7	92.0	7.5
11 Cation Exchange Resin E, Hydrogen Activated commercial sample 200 mesh	100.0	100.0	72.0	7.0	20.0	99.3
12 Cation Exchange Resin F, Carboxylic acid type commercial sample 200 mesh	98.8	72.0	98.5	97.3	100.0	15.0
13 Cation Exchange Resin G, carboxylic acid type commercial sample 200 mesh	49.0	48.0	79.5	96.0	92.0	1.5
14 Cation Exchange Resin H, Sodium Activated commercial sample 200 mesh	85.0	72.0	100.0	98.0	100.0	11.0
15 Cation Exchange Resin I, Sodium Activated commercial sample 200 mesh	81.0	78.8	92.5	96.6	100.0	17.0
16 Cation Exchange Resin I, Sodium Activated commercial sample 200 mesh	61.0	47.0	100.0	99.0	99.0	9.0
17 Colloidal Magnesium Aluminum Silicate Gel (cone, 40cc per 100cc)	24.0	14.0	71.3	96.3	61.0	4.0
18 Synthetic Magnesium Silicate	16.0	18.0	17.0	35.0	16.0	10.0
19 Synthetic Sodium Aluminum Silicate 200 mesh	19.0	23.0	62.0	98.0	64.0	none
20 High Capacity Synthetic Sodium Aluminum silicate 200 mesh	12.0	8.0	31.5	92.7	0.5	12.4
21 Polyamine Anion Exchange Resin A 10%— Synthetic Sodium Aluminum Silicate 10%— suspended in colloidal magnesium aluminum silicate gel (cone, 40cc per 100cc)	82.0	62.0	41.0	95.3	72.0	79.0
22 Activated Charcoal A	100.0	100.0	100.0	10.0	90.0	100.0
23 Activated Charcoal B	100.0	100.0	100.0	12.5	86.0	100.0
24 Activated Charcoal C	100.0	100.0	100.0	27.5	84.0	84.5
25 Activated Bauxite (essentially $Al_2O_3$ )	15.0	12.0	18.0	20.0	none	5.0
26 Fuller's Earth (essentially $SiO_2$ )	13.0	15.0	46.0	40.6	38.0	4.5
27 Diatomaceous Earth	15.0	12.0	9.0	6.0	32.0	3.7
28 Kaolin	14.0	15.0	18.0	6.7	22.0	1.7
29 Talc	12.0	12.0	15.5	none	10.0	3.0
30 Bentonite	26.4	none	89.0	95.4	99.2	3.4
31 Bauxite	16.0	16.0	14.0	3.0	none	none
32 Filtrol Adsorbent	20.0	16.0	70.0	91.7	64.0	11.0
33 Aluminum Hydroxide gel	16.0	16.0	15.0	30.0	30.0	10.0
34 Magnesium Trisilicate	14.5	20.0	77.0	97.4	44.0	5.0
35 Aluminum hydroxide powder	8.0	10.0	19.5	16.6	none	none

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## SOME GASTROINTESTINAL SYMPTOMS RESULTING FROM CARDIAC MEDICATIONS

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THE gastroenterologist is not infrequently consulted by the heart patient because of so-called indigestion, consisting of loss of appetite, nausea, vomiting, and heartburn, along with other symptoms, such as headaches, dizziness, green or yellow vision, tinnitus, vertigo, and even fainting spells attributed to the stomach. Other patients seek help because of increasing abdominal girth. The discovery of an enlarged, tender liver, if the existing heart condition, or previous heart treatment is not mentioned by the patient, may lead to an erroneous diagnosis and possibly to inadequate, even individually harmful treatment, as for instance, duodenal drainage. A third group reports frequent, small, watery bowel movements, leading to rectal irritation, hemorrhoids and so on; even incontinence of feces may occur. All these *gastrointestinal ill effects of cardiac medication* are of course known. But the patient, too often, either does not recognize the connection between treatment and symptoms, or his complaints are not seriously entertained by the physician. The gastroenterologist, then cannot be censured, if he does not immediately perceive the cause of the symptoms and initiates therapeutic measures, which must fail, because the poison is not eliminated.

There are five groups of remedies widely used in the treatment of heart disease, which may, erratically and to a varying degree, create abdominal ill effects: (1) the digitalis group, (2) the xanthine group, (3) ammonium chloride, (4) quinidine, (5) mercurial diuretics.

The following is a rather pronounced example of the necessity for reminding the gastroenterologist of the toxic effects of cardiac medication.

A female, aged twenty, consulted us because of a heart murmur, and a diagnosis of Rheumatic Heart Disease with an enlarged heart and possible Mitral Stenosis was made. She was told that she could marry, but was warned to remain under medical observation, in the event of pregnancy. After the third spontaneous miscarriage, the patient was informed that further conception would be inadvisable, and careful treatment necessary, since the heart was in a state of latent decompensation, the usual result of pregnancy in mitral stenosis. The family physician, an otolaryngologist, prescribed digitalis. When the abdomen of the rather slender woman gradually increased in girth, he advised x-ray examination of the entire gastrointestinal tract, which was reported as revealing "a sluggish liver." The patient was referred to a prominent gastroenterologist, who, during the ensuing six months, performed twelve duodenal drainages. After a two-

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year interval, the patient returned for re-examination of the cardiac status. She had the typical signs of ineffective and overzealous digitalis treatment, as well as all the symptoms of severe cardiac decompensation with both right and left sided heart failure: congested lungs, enormously enlarged liver, and a high degree of ascites. By using various drugs, the condition improved temporarily only to recur again, at which time the drugs were changed but with no better result. During a bad period, she consulted another physician who placed her on digitoxin, daily injections of mercurial diuretics, salt free diet and a large daily intake (4,000 cc.) of fluids. The patient expired within a short period.

The *toxic effect of digitalis* has been known since 1785, when Withering published the results of his ten-year experimentation with this drug, then called Withering's Infusion (42).

At the end of the last century, two forms of digitalis were in use: the powdered digitalis leaf and the digitalis infusion. The latter was reserved for the more serious situations. Twelve hours were required for its preparation and it had to be used during the ensuing twenty-four hours, day and night. If repeated for two or three days, it caused severe digitalis poisoning.

Kussmaul, in 1900 (29), called the end effect of this digitalis-infusion treatment "unexpected digitalis effect" because the toxic effect commenced suddenly, after a variable amount had been consumed and accumulated in the heart muscle. This effect was accepted as the sign of optimal digitalization and the signal to discontinue the treatment for some time. Groedel (21) had recommended, one year prior to Kussmaul, that a single large dose, with supplementary doses or multiple doses of digitalis, be used for all nonurgent cases, to eliminate the toxic effects. This method, (the so-called continuous digitalis treatment) has become widely accepted since then.

In the following decades, the goal of the pharmaceutical industry was the diminution of digitalis toxicity, for instance by eliminating the digitoxin. However, toxicity could not be completely avoided when large doses were used. This is not the place to discuss the century old dispute about the appropriate administration of digitalis. About every twenty years, the current view is reversed and pharmacologists again advocate the so-called initial full digitalization. The instances in which this routine is warranted, are few, and in all others the risk is too great, and the slow digitalis treatment is probably more advantageous. Small doses of digitalis, doses so small that the cumulative effect of the drug will not be present, may, in the presence of

valvular lesions, prevent the cardiac hypertrophy that is so common to those disorders. Star (37) has shown that 0.1 digitalis leaf, in a previously non-digitalized patient, can produce a startling improvement in the ballistocardiogram.

Patients may be irreparably injured when, in spite of the over-digitalization, the liver volume increases and bradycardia, often with frequent ventricular beats, appears. Such results are especially frequent when digitoxin has been used. This preparation was given up for about two decades and has recently, again, become the favorite digitalis drug of many clinics and practitioners. The liver tissue can be damaged by overzealous digitalis therapy. The heart muscle can be severely damaged by a single heroic digitalis dose (34).

The toxic effects of digitalis have been more frequently encountered during the past few years, since digitoxin was reintroduced and highly advocated. This is probably due to the fact that digitoxin is slowly dissipated and therefore gives prolonged and severe toxic reactions. One typical case may suffice, to demonstrate this fact:

A female, 69 years of age, was relatively healthy until 1943, when high blood pressure was discovered. Six months ago, she was found to be in congestive heart failure, was digitalized with digitoxin over a three day period, and thereafter maintained on a daily dose of 0.002. Nausea developed and one week prior to examination, after some excitement, the woman had a severe bout of vomiting with collapse, cold clammy extremities, perspiration and steno-cardiac distress. She was hospitalized. The blood pressure had fallen to 110/80; temperature (rectal) was 100°; sedimentation rate (Westergren) 13 min./hr.; W. B. C. 10,500. The electrocardiogram showed mild left axis deviation with an inverted T-I and depressed ST segments in leads II and III and the chest leads, the conduction time was prolonged to 0.24 sec. A diagnosis of possible myocardial infarction was made, and the digitoxin continued. On the second hospital day, the bradycardia (V. R. = 40) was still present. The patient only complained of nausea. When questioned about her vision, she stated that recently she had constantly noted large green spots in front of her eyes. The blood pressure returned to 150/80; a rough systolic murmur was present over the entire precordium, the electrocardiogram was similar to the preceding one. Our diagnosis was digitalis intoxication, possibly with an attendant Morgagni-Adams-Stokes attack. The digitoxin was discontinued and replaced by aminophyllin suppositories. Patient recovered quickly.

Fisher (16) showed that digitoxin, in contrast to other digitalis glucosides, becomes irreversibly fixed and accumulated in the heart muscle. The effect of digitalis on the Starling perfused cat heart cannot be removed by washing. It is quickly and firmly bound to the heart muscle (38). That is the reason why digitoxin preparations have a longer lasting digitalizing effect, and also why they lead so frequently to unexpected toxic reactions (34).

The vomiting infrequently occurring during digitalization may be of central origin. Hatcher and Eggleston (23) found that in the cat, small doses of digitalis administered intravenously lead more frequently to vomiting, than when given by mouth. Hatcher and Weiss (24) explained the reaction of the stomach to digitalis as a cardiac reflex over the sympathetic nervous system to the vomiting center. However, practical experience has shown that, in many patients, the vomiting stops when the route of administration of the digitalis preparation is changed from mouth to hypodermic injection. It, therefore, appears questionable whether the experience gained in experiments on cats can be applied to man. Furthermore, when a patient

vomits for a prolonged period, the gastrointestinal mucous membranes will finally be in a state similar to that seen in primary gastritis and absorption will become impossible. The mechanism of the emetic action of the digitalis group is still not clear and remains an academic question.

If digitalis becomes ineffective, or is not tolerated, even those who usually decline strophanthin concede to a last trial with this drug. However, because of the severe liver damage—either through chronic cardiac congestion or chronic digitalis poisoning—strophanthin, in this instance, frequently can only be temporarily successful. Fortunately, strophanthin is not absorbed in the stomach, so it must be given intravenously and the liver does not retain the remedy before it reaches the heart. Strophanthin, being much more quickly eliminated than digitalis, has fewer ill effects, if we neglect those caused by the faulty dosage of the inexperienced therapist (27).

We have seen no convincing proof that the *xanthine preparations* can cause histologically visible tissue damage. Not infrequently, however, they provoke ill effects in the gastrointestinal tract. This is known, but too frequently overlooked. Theobromine sodium acetate, even when enteric coated, is not tolerated by many patients, and may cause nausea and general ill feelings. In the presence of, or inclination to, hyperacidity, all theobromine preparations can produce a very severe heart-burn and a secondary cardiac discomfort. This can mostly be overcome by giving the medication at the beginning of a meal and prescribing some alkalizer after the meal. Aminophyllin, one of our most useful drugs, in many instances when given intravenously, is not dissolved in the acid stomach. In an unpublished study performed by the senior author some years ago, the tablets were found undissolved in the stool in about 30 percent of all cases. This can be indirectly shown by giving patients who complain of stenocardial distress and who do not improve with the oral aminophyllin, diuretin with immediate relief. The theobromine with sodium salicylate, may after very long, uninterrupted use, and only very rarely at the start of the treatment, cause frequent small watery bowel movements. If the cause is not recognized and eliminated, the condition can become intolerable, incontinence of feces may develop with markedly thrombosed hemorrhoidal veins and fistulous tracts. Proctological treatment is of no avail in such instances since the cause of the condition is not removed. On the other hand, when the theobromine with sodium-salicylate has been discontinued long enough, such patients tolerate it again, when four drops of tincture of opium are simultaneously taken with each dose.

The disagreeable effects of ammonium chloride, upon the digestive tract, are too well known to be discussed extensively. Although enteric coating of the tablets greatly diminished these, larger quantities elicit them in many sensitive patients and may make this treatment a torture. Frequently, ammonium chloride is misused, when given over a long period. The diuretic action is usually only visible when given as preparatory treatment or in combination with other diuretic drugs. Very frequently, it fails to act after longer use and then creates even more gastrointestinal distress, namely, gastritis. It also disturbs the salt equilibrium when given in that manner.

*Quinidine sulfate*, when used with the proper precautions, creates ill effects very infrequently. Some patients may show a hypersusceptibility to the drug, the most frequent sign being diarrhea. In such cases, quinine sulfate may be substituted. This was originally recommended for the treatment of cardiac arrhythmias (22). Many patients lose their hypersensitivity, when a few drops of tincture of opium are given with each dose.

*Mercurial diuretics* are not, of course, heart drugs, but are purely dehydrating agents, and act by decreasing the water and sodium reabsorption in the distal renal tubules. The first injectable preparation, novasurol (35), was quite toxic both at the site of injection as well as systemically. Bloody stools, after each injection, were a common side effect. The less toxic salyrgan was introduced by Bernheimer in 1924 (5). However, this preparation caused a great deal of local irritation and many reports of local tissue necrosis accumulated. Today, we have much less toxic mercurials which, when used with discretion and under careful observation, seldom produce ill effects. It is important to note that since the mercurials cause an increased loss of water and sodium, they may, when given too frequently, produce severe serum sodium depletion as well as acidosis and azotemia. They should not be given more frequently than twice a week unless the serum electrolyte balance is carefully watched. Daily administration of mercurials involves too great a risk. Sudden anuria, attributed erroneously to the failing heart, is frequently the end result and is often characteristically combined with abdominal cramps. Mercurials for oral administration are now available and seem effective. However, they seem to act more slowly and a greater dose is needed to achieve the same results as the injectable preparations. Their eventual harmful action on the gastrointestinal tract must still be studied. We wonder, when they suddenly fail to be effective, whether it could not be the result of mucosal damage. The few patients who complain of abdominal cramps after the administration of mercurials should be watched especially and the stool should be examined for occult blood.

Many of the previously mentioned ill effects, resulting from the oral administration of the various drugs, may be partially or entirely avoided, if the drugs are administered intravenously, thus reaching the heart directly and the liver only after having circulated through the heart.

*Digitalis* preparations were first recommended for *intravenous use* by Kottmann (28) and a year later by Fraenkel (17) and are now frequently given in emergent situations. The intravenous injection of *aminophyllin* has become a universally used treatment. Bad experiences reported with this drug are astonishing to those who, observing the rule of extremely slow rate of injection (five minutes for 10 cc. of drug) and absolute sterility, have never seen those ill effects in thousands of injections. Even a slight chill indicates faulty technique. The same statements are valid for the mercurial diuretics, provided the first injections are small and are administered very slowly.

*Quinidine dihydrochloride*, now available for intravenous use, must be given with great discretion. Groedel (22) recommended quinine dihydrochloride for emergency intravenous use. Since then, we have used various quinine preparations intravenously, in small dosages at short intervals, without any ill effects. The intravenous administration of the various cardiac remedies lead less frequently to gastrointestinal symptoms, when given over longer periods of time, but the same ill effects can ultimately appear.

For completeness, the *intramuscular application* of some of the drugs, important in the treatment of heart disease, must be mentioned. Digitalis preparations are frequently administered in this way. Mercurial diuretics, when injected deeply in the gluteus muscles, are nearly as effective as when given intravenously. *Aminophyllin*, in spite of pharmaceutical improvements, remains a painful drug when given intramuscularly; the same is true of *strophanthin*. In many instances, the absorption by the intramuscular route is slow and, therefore, the ill effects occur less frequently or much later.

One of the primary objections against parenteral heart treatment is the dependence of the patient on the physician. In the hospital, for the bedridden patient and in emergent situations, injection is far superior to the oral administration of the drug. For the prolonged treatment of a patient, this mode of administration is too great a burden in every respect. This is the only valid objection to *strophanthin* treatment, which is acclaimed by those who have had experience with it, as the most effective and scientifically best founded cardiac medication. Brams (7) after having convinced himself, at the bedside, of its safety and efficiency, recommends *strophanthin* for the treatment of heart disease. Another factor limiting the duration of chronic intravenous heart treatment is the resultant irritation of the veins. In most cases, the condition of the veins eventually necessitates a temporary interruption of the treatment.

One further route of administration of heart medication, with a minimum of ill effects, has as yet not been discussed, namely, *by rectum*. This treatment is greatly dependent on the condition of the rectum. In this regard, the cooperation of the gastroenterologist or proctologist may often be needed. Proper rectal and anal hygiene does not seem to be in general use. The development of hemorrhoids—two out of every three individuals seem to be so afflicted—could easily be prevented if simple hygienic principles are observed.

#### SUMMARY

The various drugs used for the treatment of heart disease are enumerated and their gastrointestinal ill-effects are presented. The historical background of these drugs and the reasons for their ill effects are discussed.

Note: The bibliography appears at the end of the article "History of Rectal Medication and Its Indication in Cardio-vascular Disease," this issue.

## HISTORY OF RECTAL MEDICATION AND ITS INDICATION IN CARDIOVASCULAR DISEASE

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THE inception of *rectal therapy* occurred very early in the historical past. Retention enemas were extensively used by the Babylonians and Assyrians (8). In Egypt, where the fabled tales of the holy bird Ibis were the example, there were, at the time of the Ptolemies, about 200 B.C., Enema-Specialists, who already seemed to know about the use of medication by rectal application (33). These also played a great part in the old Indian medicine and were called 'Vasti', 'Vastikarman' etc., The Greeks learned about enemas from the orient and were able to add some of their own ideas. In the works of Hippocrates (25), much is spoken about rectal applications. Various kinds of enemas, for example, honey, wine and olive oil, with some saltpeter—probably sodium nitrate—were recommended for laxative action and the removal of "phlegma" or mucus. However, true rectal therapy was also practised by the instillation of medications, which were not always completely harmless, for instance, the preparations from Daphne Mezereon. Some usages, that are practically modern, were stated by Galen (18), as for example, washing the bowel with a salt water enema followed by the immediate instillation of curative remedies. The later physicians such as Oreibasios, Alexander of Tralles and Paul of Aegina used the enema as a very important therapeutic measure (13). Nutritional enemas were also known and were recommended by Celsius (10).

The fact that suppositories, also, were commonly used by the ancient physicians may appear startling. Hippocrates recommended them in constipation accompanied by fever, especially in the weaker and young individuals, for whom the application of enemas, (the use of quantities of liquid), was not practicable. The suppositories were called Balanos and were made of honey, ox-bile, anise, and myrrh with the addition of some goose fat (26). That these were made not only for laxative purposes, but were based on multiple therapeutic considerations, is shown by the use of other drugs, such as conium, which were not infrequently harmful. It is also interesting that the ancient physicians knew about opium suppositories, and used them, as the previously mentioned Alexander of Tralles, in diarrhea. Such suppositories, named Hypotheton, were made of various types of gums and some wine, and were used only after thorough bowel cleansing with astringent solutions (1).

Rectal therapy had, therefore, a fact hardly sufficiently recognized, a very important place in the therapeutic procedures of the ancient physicians, and it is readily understandable that the Arabian physicians took over these methods. Both Rhazes and Avicenna mentioned enemas and suppositories in their works (4).

The School of Salerno knew and used enemas and suppositories and we find 'acribus Subpositoris', 'Subpositoris alterantibus', and such 'Ad Emorroides' men-

tioned (11). Arnaldus of Villanova, who was born at Valencia about 1236 and was perhaps the most important physician of the Middle Ages, transmitted the famous Verses of the *Regimen Sanitatis Salerni* in a very good form, added comments and made it known. He wrote extensively on enemas and especially on suppositories, of which he mentioned "es sapone gallica" milder ones, and stronger, sharper ones containing Euphorbium and Koloquinten. The soap suppositories are mentioned here, perhaps for the first time, and are seen in "regime sanitis" as being useful especially as a household remedy. Arnaldus mentions at that point that often healthy individuals utilize enemas and suppositories and for that reason he will write about them (3).

From the late Middle Ages to modern times, every physician made use of enemas and suppositories; these methods were obviously in common use. Some examples will show this. Jean Fernal (Fernelius (15)) ridiculed Galen and the Arabian Physicians, however, often surpassed these in the contents and complexity of the prescriptions, also those for enemas and suppositories. He, and somewhat later, the famous surgeon Wilhelm Fabry, born 1560 at Hilden near Dusseldorf and therefore often named Fabricius Hildanus, established whole enema—and suppository—systems and differentiated, according to the appearance and action, various types; the combination was often very complicated. It is worth mentioning that Fabry, as did Hippocrates previously, recommended suppositories instead of enemas for children (15).

The suggestions of Paracelsus are much simpler in this regard, since he recommended, for constipation, suppositories made of soap, while he lays less emphasis on enemas (31).

It is understandable that the pharmacopoeia present a good picture of the current thoughts and usages of their time concerning pharmaceutical-medical things and we find for example in the "Dispensatorium des Valerius Cordus" of 1556, prescriptions for "Species ad glandes aut suppositoria" (12). The Pharmacopoeia Augustana, Augsburg 1573 is very similar (32).

Sylvius and Thomas Sydenham made extensive, but careful, use of rectal medication. Sydenham discussed very accurately the qualities of the various enemata and the conditions for their use (39). It is interesting to note that Adriaan Helvetius used quinine-bark rectally, in the form of an emulsion, in 1694, while Gerhard van Swieten used a quinine-bark decoction for the same purpose (40). Boerhaave, the teacher of van Swieten, also, had recommended suppositories and enemas for various conditions (6).

With all this therapeutically effective use, there was, however, abuse of the rectal treatment, causing great ridicule of this method, the most famous being "*Le Malade Imaginaire*" by Molière, and finally decline in its use, so that it was practically forgotten at the turn of the nineteenth century. The *Pharmacopoeia Wirtenbergica* of 1750 and 1786, although the best at the time in Germany, mentioned very few suppositories, while

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the Pharmacopoeia Borussica, Frankfort, 1801 as well as 1830, mentions nothing about rectal therapy. Even in France (14) this treatment was only mentioned as an historical fact.

In 1840, impetus to the *reawakening of rectal therapy* was given by the French clinician, Andral (2) who advocated *rectal digitalis treatment*. About 1850, cocoa butter came into use as the base for suppositories, which gave even more speed to the rediscovery of this type of treatment. However, this treatment was restricted to very few drugs and its value and occasional outstanding importance greatly underestimated. The mode of action, of drugs instilled into the rectum, was not understood very well (9).

The *route of absorption of rectal medication* is barely mentioned in the literature. The rectum has a comprehensive blood supply. Blood leaves the rectum by the three hemorrhoidal veins, superior, middle and inferior. The superior hemorrhoidal veins anastomose with the inferior mesenteric vein which leads to the portal vein. The inferior and middle hemorrhoidal veins anastomose with the hypogastric and pudendal veins, which empty into the external iliac veins and then on to the inferior vena cava. Thus blood from the rectum is carried directly to the right auricle and the liver can be circumvented. The importance of rectal therapy lies in that fact. The absorption from the rectum is fairly rapid and the drug reaches the inferior vena cava without encountering venous stagnation in the liver or bowel.

Groedel (19) in 1923, mentioned that in liver congestion, ascites and congestive or drug irritation of the stomach, rectal application of digitalis, eventually together with theobromine preparations in the form of *micro-enemas or suppositories*, was indicated. Prescriptions for such rectal instillations with digitalis infusion or preparations like digipurat and for digitalis and euphyllin suppositories were given. Shortly thereafter commercially prepared digitalis suppositories appeared on the market and in the European countries, digitalis application by rectum became the method of choice for the treatment of severe chronic congestive failure.

In this country, until a few years ago, this method was hardly known by the physicians, and only recently, commercial digitalis and aminophyllin suppositories have become available. The *indications for rectal treatment of cardiacs* are still the same as those set forth by Groedel in 1923 and not only for those cases where the oral route is not possible and the parenteral administration not feasible or desirable as mentioned by White (41) and Brans (7). An enema should be avoided before rectal drug administration because it irritates and stimulates the bowel and could not be prescribed for prolonged treatment. Therapeutic drugs should be administered after a normal bowel movement; if two daily administrations are prescribed, one should be made, after a movement. That the rectum and colon absorb many soluble substances with greater or more prompt effect than by mouth, is corroborated by Sollmann (36).

*Rectal medication, therefore, is comparable in its effect, to the intravenous injection*, but can be done without the physician's constant attendance. However, absorption is slower, and in the presence of edema, somewhat more secure. The advantage of rectal over oral administration is twofold (1) The environment in the stomach is acid, that of the rectum, alkaline; and (2)

Part of the drug absorbed from the rectum is delivered directly to the heart and need not pass through, or be blocked by the liver.

*Two modes of rectal administrations* can be recommended: (a) suppositories, and (b) the micro-enema. Suppositories, especially when commercially prepared, are mostly absorbed very slowly and bowel movements should be avoided for a period of twelve hours after one has been inserted. If a bowel movement should occur earlier than two hours after insertion, another suppository should be introduced. If the anal sphincter is sensitive or tender, a small amount of nupercainol or other local anesthetic ointment should be placed on top of the suppository. This should be introduced with the small finger, covered with vaseline or nupercainol, up to a point where it is no longer felt. Because of the slower absorption, larger doses can be given than parenterally, without risk. The rectal absorption of suppositories is slowed down also, because the vehicle used melts rather slowly at body temperature. If much quicker absorption is desired, the micro-enema is preferable.

The technique most suitable for the micro-enema was explained by Groedel (19). The drug to be introduced must be dissolved in 10 cc. of lukewarm water and 3 to 5 drops of tincture of opium may be added each time if needed. If several drugs are to be given simultaneously, for instance strophanthin and aminophyllin, the mixture of the drugs should be made first. The 10 cc. of fluid to be instilled are drawn into a 10 cc. syringe; a three inch piece of thin rubber tubing, preferably a piece of a number 8 or 10 catheter, is attached to the syringe, and lubricated slightly. The patient, while recumbent, can easily insert the catheter to its end and empty the contents of the syringe into the rectum. The technique is simple and can be mastered by any patient especially when instructed practically by the physician or a nurse. For some drugs, which in concentrated form act irritating, the micro-enema may be the method of choice. If aminophyllin suppositories cause a burning sensation in the rectum, the drug will be well tolerated as a micro-enema, especially when three to five drops of tincture of opium are added each time. Digitalis never seems to be irritating. However, since the absorption of rectal medication is slow, strophanthin, as the superior drug, can be given without any risk, and is preferable for all those patients who are in severe congestive heart failure.

The hygienic rules, which should be observed by every healthy individual, must be explained to the patient who is to be given rectal medication. After each bowel movement, the skin should be sponged with mild soap and warm water and then dried with very soft tissues. The slightest irritation should be treated externally, and eventually internally, with nupercainol or similar ointments. A proctologist should be consulted in the presence of chronic irritations. Hemorrhoids, if not too large or badly inflamed, are no impediment; they frequently improve through the opium administration with the enema. Once in a while the route of administration may be changed, especially if the rectum is sensitive.

Large enemas are useless as vehicles for cardiac medication. In roentgen studies performed by Lossen (30), it was demonstrated that even quantities as small as 150 cc. are retrogradely transported through the

colon. Thus the medication given by large enemas would go into the portal system. The use of only 10 cc. of fluid guarantees retention in the ampulla of the rectum.

Groedel (20) reported, in 1935, on the alternating treatment by oral, intravenous and rectal digitalis treatment, in the same patients. Since then we have followed numerous patients for several years under rectal strophanthin treatment. The dosage required was found to be between 0.0005 and 0.001, usually, but not always, given twice daily. One case may suffice as an illustration.

The female, aged 35, suffers from rheumatic heart disease with an enlarged heart and mitral stenosis and insufficiency. When first seen, nine years ago, she also had a complete heart block and severe bouts of ectopic ventricular tachycardia with Morgagni-Adams-Stokes syncope attacks. It had been previously discovered that even the smallest dose of digitalis caused nausea and tachycardia. After a short period of observation, strophanthin was given rectally and 0.2 quinidine sulfate orally. After approximately two years, the heart returned to normal sinus rhythm. The paroxysmal attacks of ventricular tachycardia have never recurred. Discontinuation of either the quinidine or the strophanthin for a forty-eight hour period leads to irregular heart failure. The patient married, had an uneventful therapeutic abortion and as long as she is under treatment, has been free of subjective or objective symptoms of failure and has been fully active in her housework.

#### SUMMARY

The history of rectal therapy, the route of absorption, and the methods employed, are discussed extensively and the indications for such therapy are presented.

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## THE TENDENCY TO RUMINATION

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THE psychological impulses which are transmitted via the autonomic nervous system and expressed by special behavior of the digestive system from infancy onwards have been analyzed by Alexander (1) (2). Kubie (6) and others have assumed the existence of a

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"biochemical nucleus of the instincts" which acts upon the inherited though plastic synaptic patterns.

The various oral impulses,—aggressive, receptive, sensual, rejective,—undoubtedly play an important role in producing various forms of gastric neurosis, once the

original drives are suppressed or frustrated. The actual events of life are the precipitating factors in such neuroses, and they occur only in emotionally immature persons. The basic dynamism of personality is that very antagonism which must exist between the obligatory needs of the ego on the one hand and its own inhibitions on the other. Essentially these needs and inhibitions are compulsive and phobic in character, but we rationalize them as free choices in the moral and esthetic fields. While this is distinctly a "psychoanalytical" philosophy of life, it is forced upon us by profound consideration of the psychic facts evidenced in everyone's behavior. Gradual adaptation and development from infancy onward produce an accumulation of energy in the unconscious which we may regard as being incorporated in units known as "complexes." It may be assumed that most of the material in the unconscious has been evolved through successful integration, but those complexes which have escaped integration are projected into adult life, always in symbolic form (11).

In infancy, "repetitive activity" is a universal phenomenon without which primitive identifications would be impossible. We conceive of *ruminatio*,—a physical event—as having its psychic counterpart, and both enter universally into our basic, obsessive-compulsive natures. Each individual however preserves unique dynamic aspects of his own and it is always hard to decide if these are hereditary or acquired (10).

#### THE RUMINATIVE COMPONENTS

The impulse to breast feeding is partly tissue hunger and partly oral sensualism. Normal eructation,—the "after feeding"—occurs as a result of complete satiation. The regurgitated milk brings a new taste satisfaction and the baby usually swallows the portion not expelled. Under unpleasant environmental conditions vomiting becomes an expression of dissatisfaction and represents an aggressive-rejective reaction.

Conscious as well as unconscious conflicts are produced in children by the restrictions which society imposes upon the erstwhile unrestricted ego, and out of these very conflicts emerge at length hostility, jealousy, hate, guilt, repentance, remorse, and so on. Should these conflicts be repressed, they may express themselves in the somatic behavior of the digestive system and give rise to such symptoms as anorexia, vomiting and rumination.

While rumination is considered by some authors (4) (7) (3) as quite normal, this view is debatable since rumination is not universal. Indeed, when it does occur, the underlying causes should be investigated (5). The tendency to rumination seen frequently in children, must in the case of adults be regarded as an expression of some conditioned reflex originating since childhood. Eructation and regurgitation, as components of the ruminative tendency, could profitably be studied as a contribution to our knowledge of various dyspeptic disorders. Wear (9) feels that the pediatrician is in an advantageous position for discovering the early disturbances which result in the conditions dealt with by the gastroenterologist.

Eructation is always due to swallowed air (8) except in instances of pyloric block with gastric fermentation. Air swallowing is not an uncommon phenomenon, but in severe instances we feel that voluminous eructations symbolize the ejection of accumulated emotional ten-

sion. The psychiatric meaning of regurgitation is incomplete rejection, yet in some cases it involves a re-tasting of the food, as though to symbolize the conscious mind sampling what has been raised from the depths. When regurgitated food is remasticated and reswallowed we are then dealing with true rumination.

The ruminant person usually eats hastily and inattentively, drinks excess of liquids with or soon after meals, is emotionally unstable and completely lacks the gourmet's discrimination. (6) He meets life passively and it is only through repetition and re-elaboration of his concepts that he comes to understand experience. To his anxiety he adds a pattern of compulsive mental rumination. He has no tendency to complete rejection. He merely strives, as best he can, to convert unpleasant situations into tolerable ones. We also feel that he lends himself to oral erotic fixation.

#### CASE REPORTS\*

Three illustrative cases are presented,—one of simple reflex cardiospasm with true rumination, one showing an obsessive ruminative tendency, and one of globus hystericus with the same tendency.

*Case 1.* A 48-year-old multiparous woman presented the common menopausal symptoms,—chilliness, hot flashes, sweating and a digestive complaint consisting of intermittent dysphagia and rumination. She said that the first food bolus descended with some difficulty, the second more easily and from then on no difficulty in swallowing was experienced. Before finishing the meal, however, dysphagia reappeared forcing her to eat hurriedly in order to complete the meal while she could still swallow. After the meal, epigastric fullness and bloating persisted for 30 minutes, followed by rumination about every 3 or 4 minutes. This consisted of an initial belch, food regurgitation, and then remastication and re-swallowing.

Careful radiological studies showed no achalasia or other abnormalities of the upper digestive tract. She might easily have been diagnosed as "nervous reflex cardiospasm associated with the menopause" and have been reassured that nothing was wrong, yet even a superficial psychological investigation would have revealed the true cause of her symptoms. She presented a father dependent personality with an idealized Oedipus complex. Her husband though older than she, had previously been associated with a young woman of lower social status and very questionable morality. The patient had always loved and respected her husband, identifying him with her own cultured and virtuous father, so that upon being informed of her spouse's unfaithfulness, she experienced a sudden profound psychic trauma, which gave rise to insoluble conflicts. She was in the position of being unable to "drink the bitter cup" or to reject the unpleasant situation. Her frustration and re-elaborated complexes were thus first projected as cardiospasm and then as rumination.

*Case 2.* A 44-year-old man complained of post-prandial epigastric fullness with gaseous eructation and regurgitation of liquid with small food particles. The regurgitated material, being neither sour nor offensive, was sometimes expelled and sometimes re-swallowed. X ray examination of the upper digestive tract was negative.

Emotionally he was a nonresistant, extroverted individual with repressed hostility toward his father and to a lesser degree toward his mother, brothers and sisters. His father had never believed him to be his own son, and had accused his wife of unfaithfulness. The mother denied the accusation, but in order to appease her husband, adopted a frigid attitude toward the unfortunate son. Since the age of 12 he had been obliged to work and hand over his earnings to the family. Not until 1939 was he able to earn enough to live without privation.

\*The first case has been taken from the author's monograph on "The Psychosomatic View of Disorders of the Digestive System," (pp 54-55) 1948, printed in the Hellenic language. The second and third cases are from the G. I. Clinic, Notre Dame Hospital, Montreal, where the author recently worked.

He longed for a better social status, studied languages, and wished to become an artist.

Although now employed as a pastry salesman he enjoys history, philosophy and art, and feels that he would be happy were he in business for himself. In spite of his ambition and perfectionism, luck has always been against him, and his chief personality characteristics are a feeling of profound insecurity and a severely critical attitude toward parents, employers and social institutions. Through a tendency to rumination, his obsessive fantasies and compulsive-phobic reaction found expression in the digestive system. He thus symbolized his realization and attempt at readaptation.

*Case 3.* A 28-year-old woman, presented the classical symptoms of globus hystericus, complained also of regurgitation of liquids and small food particles, which after being tasted were swallowed again. The x-ray studies were not helpful. She had an unhappy marriage in that she could not see in her husband the ideal man of her dreams. A regressive complex resulted and she returned to the phyletically earlier satisfactions of oral erotic fantasies. This conversion of emotional tension into a peculiar somatic response must be viewed as a primitive type of compromise and re-elaboration, and indicates her essential immaturity.

#### CONCLUSION

The tendency to rumination is a universal phenomenon in infants, and its persistence in adult life indicates the somatic projection of psychic conflicts as well as emotional immaturity and sometimes distinct regression. True rumination is rare, although the *tendency to rumination* may be observed in gastric neuroses and peptic ulcer, especially in persons having personality difficulties. The physician should investigate the emotional conflicts of these patients and assist in correcting

the reactions. The obsessive-compulsive psychodynamic reaction must be analyzed even in the presence of conversion-hysteria symptoms.

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# NUTRITION

## SOME DIETARY PRINCIPLES IN DIGESTIVE DISEASES

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“INSTEAD of a diet for every disease, the trend is to have a diet which has certain therapeutic principles that can be applied with only slight modifications to a number of different diseases.” Since Doris Johnson (1) expressed this concept, the dietary management of diseases of the stomach and intestine has taken on interesting new meanings, and has been considerably simplified.

#### GENERAL PRINCIPLES

Usually the patient is fed by mouth, but in the unconscious, sometimes in anorexia nervosa, as well as in refractory patients and those unable to eat or swallow in a normal manner, the nasal or stomach tube is resorted to. Intravenous and rectal feeding will not be discussed.

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So far as *texture* is concerned, food may be offered in several forms,—full or regular diet, light or convalescent, soft or pureed and liquid or fluid diet. Thus a patient may be on a regular ulcer diet, light ulcer diet, or liquid ulcer diet. These terms describe merely the consistency of the food, without reference to quantity.

Feeding *intervals* vary. Food and fluids may be offered more frequently than every two hours, or less frequently than three times daily. When fluids require to be forced, as much as 5000 c.c. daily may be consumed through the simple plan of offering fluids every 30 minutes. Ordinary diets are estimated to contain 1 c.c. of water for each calorie.

#### THE NORMAL DIET

Many disorders of the digestive tract do not require any modification of the so-called normal, or “house full diet.” Being a mixed, varied and alternating regime, it satisfies the requirements. Certain foods of the onion and cabbage families are restricted on full hospital diets

because they so readily ferment and are difficult to digest even when cooked by special techniques. The patient's individual food habits and preferences ought, when possible, to be respected, for one of the prime requisites of any diet is its acceptability. Among the irritating substances which are to be eliminated from the normal diet are burned foods, condiments, spices, concentrated sugar, strongly flavored or coarse vegetables, excessive fat, particularly superheated, decomposed or rancid fats, as well as excessive amounts of lignin and cellulose.

As to *quantity*, the patient should be fed in accordance with his weight. I have described routine hospital diets elsewhere (2), and, while ideal weight tables are valuable, we may roughly estimate the fuel needs of a patient confined to bed as from 1600 to 2100 calories per diem. The normal diet may need to be temporarily altered following food binges or upon the appearance of food intolerances or food allergies or dyspepsia of undetermined causation.

In placing a patient on *any kind of special diet*, it is highly important that he should be definitely informed as to how long a time the special diet is to be employed, for it is a rather common experience to encounter an individual who has remained on a restricted diet for as long as four years, much to his own disadvantage if not actual injury. Obviously, a chronic diet which cannot keep a well person well will surely make a sick person worse. One should be on guard also against prescribing or permitting foolish and senseless diets, for the practice is not too uncommon. A patient on my ward some years ago was ordered to receive a liquid diet for 30 days although both the patient and the dietitian questioned the *rationale* of a very limited protein, mineral and vitamin intake, prescribed apparently for no obvious reason whatever. I have noticed that the most successful physicians have a characteristic habit of permitting their patients "something to eat" under most circumstances. A good rule is that, if a liquid diet is to be used for longer than 10 days, it should receive supplementation to make up for limitations which can become serious.

#### THE BLAND DIET

The bland diet is the one most commonly employed for convalescent enteritis, gastritis, typhoid fever, the diarrhea of food poisoning, pernicious anemia associated with diarrhea, full-blown pellagra, thyrotoxicosis with intestinal symptoms, parasitic infestations, bacillary dysentery, pancreatitis and regional ileitis. The essential principle of the bland diet is the daily repetition of even quantities of mild foods without chemical, mechanical, thermal, bacteriological or toxic irritants. The bland diet is considered to be at times indicated in peptic ulcer, hyperchlorhydria, gastritis, and cancer of the stomach. The *modified* bland or smooth diet is employed in spastic constipation, diarrhea, colitis, diverticulosis, hemorrhoids, partial obstruction of the gut, enteritis, dysentery and following certain intestinal operations.

The ideas behind the bland diet are numerous and they are aimed at relieving and preventing all types of irritation. To this end, low residue foods are employed, peptic substances are reduced, and the lignin content is limited. Organic acids are diluted, sodium

chloride intake is cut down, temperature extremes are carefully avoided, food volume is reduced by cooking, and highly flavored materials are used sparingly. Secretagogues, such as are found in certain beverages, particularly tea, coffee, coca-cola and postum are eliminated. The coarse hull and husk of entire grains is milled off. A mixed diet is provided containing fewer kinds of foods at each meal but more variety over a longer period. Such stimulating foods as mushrooms and meat extracts are definitely reduced. Fat is emulsified, tough portions of plants are discarded, and the total bulk of the individual meal reduced to 6 or 8 grams. Protective foods and sufficient vitamins and minerals are necessary, and proteins containing the essential amino acids are included. The clinician, in ordering a bland diet, ought to have valid clinical and laboratory evidence to support the prescription. He should also recognize individual tastes on the part of the patient and ensure that the patient understands the methods of food selection and food preparation, should the diet need to be continued over long periods.

#### ULCER DIETS

Many ideas have been proposed for the dietary management of peptic ulcer, but none of them can be regarded as final or perfectly efficacious. Delairo (6) has emphasized the importance of such non-dietary factors as rest, fresh air and a healthy upper respiratory tract in the treatment of ulcer. Lasher (7) and a host of others have stressed the psychosomatic factors needing adjustment. Bernstein (8) suggests that the pain of ulcer may be of vascular origin. Steele (9) as well as the majority of physicians are opposed to all reducing or impoverished diets in peptic ulcer. The ulcer regimes of Sippy, of Ochsner and of Coleman are well-known. Roth (10) (11) and others have indicated that caffeine may play an etiological rôle in the disease. A test meal for gastric analysis using caffeine has been described by Musick *et al* (11a). Smoking is thought by some to nullify the effects of antacids and to interfere with the utilization of vitamin C. Among the ulcer patients in our clinic we find fewer exacerbations and recurrences among nonsmokers.

Protein foods are used not only for their buffering action against free HCl, but also to provide the essential amino acids. The Meulengracht diet (12) (13) enjoys some popularity for these very reasons. Sufficient protein must be provided to meet the body needs as well as promote healing. It is well to bear in mind the equivalent protein values of various food stuffs. Thus, 200 gms. of lean meat provide 60 gms. protein, or the same amount of protein can be obtained from various plant and dairy sources as follows,—250 gms. of yellow cheese, 175 gms. of soybeans, 290 gms. of garbanzas, 135 gms. of low-fat soy flour, 165 gms. of full-fat soy flour, 120 gms. of defatted peanut flour, 170 gms. of skim milk powder, 320 gms. of cottage cheese, 150 gms. of defatted almond meal, 240 gms. of wheat germ flour, 420 gms. of corn germ flour, 420 gms. of Brazil nut paste, or 130 gms. of dried brewer's yeast.

Where small, frequent, low residue, non-irritating feedings are needed throughout the day, one may use a modified bland diet composed of milk, eggs, soft unfermented cheeses, non-gas-forming cooked vegetables, low-acid and seedless fruits without the skins, milled grains, powdered defatted nuts, low-fiber seedmeal

flours or legume flours, meats without fibrous tissue, limited amounts of carbohydrates and decreased total fat.

For patients requiring supplements via the stomach tube, high caloric mixtures may have added to them,—alacta, amigens, aminoids, brewer's yeast, casec, dietene, dryco, klim, powdered milk, soybean flour, seedmeal or legume flours, defatted nut flours and other commercially available protein concentrates.

Dietary concepts in *gastritis* have been described by Schindler (14) (15). Perhaps the modified bland diet, with increased fresh foods, limited condiments, added vitamin A and foods containing the "extrinsic factor" is a good rule of thumb for patients with chronic gastritis.

In *hypomotility* following operations or illness, and in the gastric stasis of partial pyloric block, one must offer foods that are easily digested without vigorous mastication. Fluids with meals should be limited to one-third of a cup.

In *achlorhydria* associated with gastric neoplasm or pernicious anemia, particularly when symptom-producing gastritis is present, fermentable foods such as those high in cellulose or sugar may be restricted.

In simple *hyperacidity*, protein buffers to combine with the acid are used along with antacids (16) while spices, condiments and secretagogues are avoided.

#### DIARRHEA AND CONSTIPATION

In *acute enteritis*, whatever its cause, food is withheld the first day, and only hot tea or water offered. Later, cooked rice, toast, potato without milk, and milled cereals without sugar or milk may be used, with very gradual restoration of fruits, vegetables, and proteins as the patient's condition permits.

*Ulcerative colitis* may, for short intervals, respond to any of several dietary measures. We know that we must use nonfibrous foods, a very high protein intake to produce a positive nitrogen balance, and a high intake of vitamins A, K, C and rutin. Start on a non-residue diet and gradually work up to a low residue diet, but with restriction of potato, lactose-containing foods and sugar. A smooth-puree diet is not advisable if the patient is a good masticator.

Lahey (17) and Best (18) have described the colostomy regime. One starts with large portions of milled cereal, hard-cooked egg, dry toast without bran, boiled milk, cream soup containing strained vegetables (except greens or carrots), creamed fish or meat, baked or mashed potato, boiled rice or custard, scalloped cooked vegetables (except beans, spinach, carrots, greens, tomato or gas-formers). Limited amounts of soft custards are permitted, as well as junket, plain white crackers, dry cottage cheese, sponge and angel-food cake. No raw foods, no fruits and no whole grains should be used. The foods which are known to be capable of causing diarrhea are,—grape juice, raisins, corn, baked beans, fried foods, prunes, prune juice, apricots, eggs, orange, orange juice, condiments, onions, melons, cabbage, alcoholic drinks, carbonated beverages, fish, especially shell-fish, maple syrup, and exceedingly salty foods.

*Diarrhea* also may be caused by drugs, lack of HCl, emotional upsets, bacterial invasion and over-emphasis on certain foods. During diarrhea, salt, protein and

fluids are lost. In treatment, water and mineral losses should be early restored but the diet should be light and non-stimulating. In acute inflammatory diarrhea, a bland, high protein diet is called for. Boiled milk (if tolerated, and if it does not prove to be a distinct laxative) may be used and gradually increased. Dietary regulation must follow the progress of the patient's digestive powers, and the Schmidt test for food utilization is simple and valuable,—a diet of cooked round steak, chopped or mashed potato, milk, egg, and heavily buttered white bread are used, and a 3-day stool specimen is examined for gross starch, fat and meat fiber.

*Constipation* due to any form of obstruction or resulting from surgical procedures, should be treated for short periods of time by a non-residue diet. (Constipation resulting from a non-residue diet itself often is desirable following rectal or perineal surgery). A very strict non-residue diet consists of boiled rice, milled cereals, dry cottage cheese, ground or scraped beef, boiled eggs, white toast, jelly, tea and sugar in limited amounts, with prohibition of fruits, vegetables and milk. Where constipation is the result of long-continued laxative habit, dietary ignorance, excessive irritants, or complicated by colitis, the diet should start with a bland, soft-solid regime and work up gradually to a general mixed, full diet. *Atonic constipation* due to lack of exercise, faulty diet, repeated abdominal operations, irregular bowel habits, congestion or constitutional disease such as hypothyroidism, responds best to an increase in the roughage,—lignin, cellulose, and hemicellulose. Normal diets contain 6 to 8 gms. of cellulose, while high residue diets contain up to 12 gms. Brewer's yeast, while not contributing to the residue, is a valuable adjunct to constipation routines. The patient should greatly increase his water intake and establish regular and effective bowel habits.

#### DIETS IN VARIOUS GASTROINTESTINAL DISORDERS

In *food poisoning* and *ptomaine poisoning*, limited food intake is advisable until the offending substances are removed. Foods which combine with the poison or which help to alter the bacterial flora are at times of value. Sometimes *foreign bodies*, such as open safety pins are apparently assisted on their way through the tract by feeding a dry diet of potato, bread and thick cereal. In *tropical sprue* as well as in *idiopathic steatorrhea*, it is advisable to use a low fat, bland diet, rather low in concentrated carbohydrates, high in protein (over 20 per cent of the total calories), high in vitamins and minerals with enzyme supplements (e.g., pancreatin) and crude liver extract parenterally. In the *celiac syndrome* the child under 8 years of age should receive protein milk with added casein up to the levels of 10 to 20 gms. of protein per kilogram of body weight per diem. After 8 years of age this is lowered to 8 gms. of protein per kilogram. The child often loses from 20 to 60 percent of the dietary fat, from 10 to 15 percent of the carbohydrate, and from 20 to 65 percent of the protein,—hence the need for high caloric intakes. In *chronic cystic fibrosis* with early onset of pancreatic insufficiency, carbohydrates are limited to the less readily fermenting types. *Carbohydrate intolerance* may be encountered in gastrocholic fistula and in chronic mechanical obstruction of the bowel, but the patient should not be given less than 125 gms. of carbohydrate daily in any case, so that he may meet his daily sugar needs.

In *diverticulosis* and *diverticulitis*, it is well to use a modified high residue diet with a laxative effect. This can be done by increasing the portions of fruits and vegetables and fruit juices containing organic acids. To be avoided are,—corn, beans, onions, cabbage, old tough vegetables, nuts, bran, husks, peelings, skins, berries with sharp seeds such as boysenberries, entire-grain coarse bread with whole kernels or seeds such as caraway, poppy, sesame, or dill seeds.

In neoplasms producing *edema of the stomach or peritoneum*, it may be desirable to use a bland, low sodium diet (25) in an effort to get rid of retained water. While such a diet presents some difficulty, it may incorporate the following food stuffs: distilled water, milk with the sodium removed, unsalted almond paste, sweet apple juice, baked apples minus the skin, canned applesauce, cooked peeled apricot, asparagus tips frozen or freshly cooked in distilled water, very ripe avocado, banana, pearl barley, green beans frozen in cooked in distilled water, green hulled lima beans similarly cooked, occasional beets, berry juice, limited amounts of nut flours, salt-free bread, plain salt-free rolls, unleavened bread and salt-free or sweet butter, 300 c. c. amounts of buttermilk. If lonaflac or other dialyzed milk is not available, use skim milk, making up the protein deficit by incorporating soybean flour into the cooked cereals. Cottage cheese and hoop cheese have less sodium than American cheese or cured cheeses. Other foods which may be used include carrot, white Royal Anne cherries, strained fresh sweet corn, egg, farina, limited amounts of plain gelatin dessert made up with fruit juices, avoiding the packaged products which sometimes contain sodium citrate in flavors, fresh water fish, fresh cooked beef, lamb, mutton, veal or chicken, plain wheat gluten, strained oatmeal, limited amounts of oil, fresh orange, grapefruit and lemon juice, tomato juice made by cooking fresh tomatoes in distilled water, peaches, pears, pineapple juice, potato, yams, pumpkin, converted and white rice, puffed rice, puffed wheat, shredded wheat, muffets, squash of all kinds, fresh tangerine juice, cooked milled cereals, yellow cornmeal, wheat germ flour, strained lentils and garbanzas in homemade cream soup, macaroni, spaghetti, homemade noodles, strained peas if mature, strained green soybeans and fresh persimmons.

In feeding *post-operative patients*, gas-formers should be omitted such as soda biscuits or other foods in the quickbread-batter-and-dough line with enmeshed and trapped gas which expands in the intestinal tract; cauliflower, brussels sprouts, onions, cabbage, baked beans, superheated fats, greasy or spicy foods, whipped foods such as souffle, mashed potatoes, whipped cream, whipped jello, merimenes, and sugary foods. Heavy peelings and foods high in raw pectic substances should be limited.

In all diets one should keep in mind the recommended daily allowances for the individual (19 to 24).

#### SUMMARY

Every therapeutic diet should approximate normal and optimal nutrition as nearly as possible and lead back to as nearly a full diet as can be accepted. Both hospital patients and out-patients require a well-thought-out and individually-constructed basic food program which recognizes as far as possible the tastes and idiosyncrasies of the person himself.

The gastrointestinal patient who is out of control ordinarily presents a confused and frustrated personality, and part of his "diet" should consist of psychotherapeutic tid-bits and even substantial sermons. Confering upon him the power of self-help should be the constant purpose of each professional contact. Without psychosomatic adjustments, diets by themselves may prove only partially effective.

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## ABSTRACTS ON NUTRITION

HANKS, R. J.: *Cod liver oil therapy of tuberculous empyema.* (Texas State J. M., May 1949, No. 45, No. 5, 290-295).

The author treated 4 cases of tuberculous empyema complicating pneumothorax by means of intrapleural injections of cod liver oil which had been sterilized by passage through Berkefeld filters, and subsequently shown not to have lost its vit. A and D potency. The patients markedly improved. Tubercle bacilli disappeared from the exudate which became clear and reduced in amount. Thoracoplasty was thus avoided. Every two weeks, for a period of 6 months, following aspiration of pus, 20 c.c. of the vitamin D concentrate were instilled into the pleural cavity. The method appears to have promise and may depend upon a bacteriostatic action of the cod liver oil.

STEINER, A., KENDALL, F. E. and BEVANS, M.: *Production of arteriosclerosis in dogs by cholesterol and thiouracil feeding.* (American Heart J., July 1949, Vol. 38, No. 1, 34-42).

This work is a confirmation of the fact that arteriosclerosis can be produced in the dog by the combined feeding of cholesterol and thiouracil. The lesions were found to have the same anatomical distribution and sites of predilection as do lesions in man, including the occurrence of cerebral arteriosclerosis. The intimal infiltration with foam cells and endothelial proliferation of the early lesion as well as the hyalinization, hemorrhage and calcification of the later stages, as seen in man, were duplicated in dogs. Thiouracil in the dosage employed does not lead to arterial lesions. In one dog, cholesterol feeding without thiouracil produced early arteriosclerosis. (This work forms a remarkable complement to that of Dauber, Horlick and Katz who found that desiccated thyroid protected the chicken from arteriosclerosis.—Reviewer).

KINNEAR, A. A. and KEEN, E. N.: *Oral protein hydrolysate in pulmonary tuberculosis.* (Am. Rev. Tuberculosis, May 1949, Vol. 59, No. 5, 511-518).

38 patients with pulmonary tuberculosis were divided into two equal groups. One group received an additional dietary supplement of 50 grams of protein hydrolysate per day. The results of this treatment were gauged by clinical, x-ray and biochemical methods. During the six-week period of observation, no beneficial effects of statistical significance were noted which could be attributed to the increased protein in the diet.

SHUTE, W. E., SHUTE, E. V. and VOGELSONG, A.: *The physiological and biochemical basis for the use of vitamin E in cardiovascular disease.* (Ann. Int. Med., May 1949, 1004-1008).

The authors first point out that the original conception of vitamin E as a preservative of precarious pregnancies coincided with the discovery of the tocopherols, but today it is known that they exert an influence on general metabolism, particularly the muscles. These facts seem well documented by veterinary cardiology as well. Then the authors emphasize that they are using alpha tocopherol, not as a vitamin supplement at all, but in massive doses for its pharmacodynamic effect on the heart in cardiovascular disease.

CAMPBELL, D. A. and TONKS, E. L.: *Vitamin A, total carotenoids, and thymol turbidity levels in plasma.* (Brit. Med. J. Dec. 31, 1949, 1499-1501).

In a series of tests on 133 normal adults living in the English Midlands during 1947, it was found that the average blood levels of the total carotenoids and of vitamin A were lower than those found in other countries. This is partly due to the lack of fats in England and a national distaste for large quantities of green vegetables and salads. In the series, 85 percent of the cases had carotenoid values in the plasma lying between 40 and 120 micrograms per 100 cc., and vitamin A levels between 80 and 130 i.u. per 100 cc. Vitamin A levels

showed a slight fluctuation during the year, while the total carotenoids rose steadily from March to December. Subjects performing hard manual work showed lower levels of both than subjects engaged in sedentary occupations. Thymol turbidity tests were performed on 110 normal adults and when allowance was made for a "blank" test, the normal range was 0 to 1.5 c. c. of barium sulfate suspension.

MAYER, J. and SCOTT, M. L.: *Nutrition on the international plane: the nutrition division of F A O.* Nutrition Reviews, 1949, 7, 11, 321-327.

The Food and Agricultural Organization (F A O), began at Quebec in 1945. It has always emphasized nutrition and given a central position to its activities. The Council of F A O (World Food Council) carries on the work between sessions and directs the policy of the International Emergency Food Committee (I E F C) which undertakes to distribute scarce agricultural commodities wherever needed in the world. The Nutrition Division of F A O ensures that modern concepts of nutrition underlie all F A O activities and bring these to the attention of the governments of the 58 nation members. Mass assessment of nutritional status through surveys is encouraged. Special attention is given to food technology, such as methods of processing and preservation which best can utilize the available food resources of undeveloped areas. Nutrition projects of a practical kind have been and others soon will be conducted in the Philippines, Latin America, the far East, Central Africa, Europe and the middle East. The Nutrition Section of the World Health Organization (W H O) is more concerned with the clinical aspects of nutrition and the place of malnutrition in the pathogenesis of other diseases. F A O has no research facilities. The central problem involved in establishing a picture of world nutrition is that of correlating the per capita supply of each food, the results of dietary surveys and the mass assessments of nutritional status. The role of environment in relation to dietary requirements has not as yet been satisfactorily studied. The aim of F A O is the world-wide planning of food and agricultural programs, and its success will depend on agreement with respect to quantitative data on human needs in varying circumstances.

BASIL-JONES, B. J.: *Diabetes in pregnancy: Laboratory assistance.* (Med. J. Australia, Oct. 15, 1949, 558-564).

The diagnosis of diabetes in pregnancy requires an estimation of the patient's glucose tolerance. A type of dextrose tolerance which fails to fall to 110 mg. or less in 3 hours may be found in pre-diabetic women. Unexplained intra-uterine death of a fetus of greater than average size ought to arouse suspicion of a diabetic inheritance in the mother. Maintenance of equilibrium among the sex hormones is needed to insure continuance of pregnancy and fetal survival. Examination of vaginal smears offers a simple, though only approximate method of control of endocrine therapy. In prediabetic women, the use of hormones results in an improved fetal survival rate.

SHEUMACK, D. R.: *Diabetes mellitus and pregnancy.* (Med. J. Australia, Oct. 15, 1949, 553-558).

The original material of the author showed 45 cases of diabetes associated with pregnancy out of a total of almost 39,000 confinements. This exceeds Joslin's estimate that about one woman in 1000 of childbearing age is diabetic. Insulin increased the fertility of diabetic women. Careful diet insulin management with induction of labor or the performance of Caesarean section at about the 38th week results in viable babies in almost a normal number of instances. Deformity of babies, and their oversized stature and their edema, all of which contribute to their high death rate soon after birth, probably are due to the obvious fact that the mother's pituitary gland is deeply involved in a diabetic pregnancy. In the mother, sugar tolerance frequently is diminished and the renal threshold for sugar also is lowered. During the puerperium the insulin dosage may usually be reduced. The mother also shows increased tendency to ketosis, water retention and usually to imbalance of sex hormones. Progesterone and stilbestrol were used daily in such cases.

The infant's bronchial tree at birth is nearly always full of inhaled amniotic fluid which requires immediate suction, but the infant really does not need glucose injections.

TODD, RAMONA L.: *Results of reducing diets for over-weight university students.* Journal Lancet Dec. 1949, 69, 12, 429-30.

In treating 364 persons for obesity, basal metabolic readings were done on 172 of them, the tests revealing that 24.4 per cent had rates of minus 11 or below. Yet practically the same findings were obtained in a control group of 148 individuals who were not overweight, 23.9 per cent having rates of minus 11 or below. No correlation was found between the B. M. R. and the degree of fatness or leanness of the persons examined. In reducing women did somewhat better than men. Dexedrine seemed to assist in obtaining greater weight loss in the first month in 23 of the women on whom it was used. Apparently thyroid extract was not used,—merely dietary measures.

SCHOTT, A.: *Cardiac pain due to glucose deficiency.* Proc. Royal Soc. Med. Nov. 1949, 42, 861-862.

A case is described of a woman aged 43 who suffered from chest pains resembling angina which were relieved by taking glucose. The glucose tolerance test showed a dip to 80 mg. at 2 hours. During attacks, cardiographic abnormalities were present. Frequent meals containing as much protein as possible have done away with her attacks.

SABHESAN, D. K.: *Peptic ulcer in South India.* J. Indian Med. Assn. Oct. 1949, 19, 1, 3-9.

Sabhesan, while recognizing the obvious importance of acid pepsin secretion and the currently-popular importance of emotional factors in causation of peptic ulcer, lays great stress also, particularly in South India, on the role played by undernutrition. People in this area usually live on food intakes of very low caloric value (1200 to 1400 cal. per diem) and with very little protein or animal fat. Rationing now is enforced, but even prior to rationing the highest caloric intake was 1921 calories consumed by the "middle class non-vegetarians", while the highest intake by the farmer and laborer in the Travancore region was 1564 calories. Even among the middle classes, the best sources of protein were rice and buttermilk, while meat was very scarce. Today conditions are much worse because of rationing. Fibrotic lesions of the liver are commonly seen at operations for ulcer in India. Consequently the author feels that malnutrition, associated with hepatic cirrhosis must be regarded, in India at least, as an etiological syndrome in the pathogenesis of peptic ulcer. How frequently the diagnosis of ulcer was confirmed by x-ray he does not state. Medical treatment resembles closely that which is universally employed. In surgical treatment, partial gastrectomy is favored. Owing to the usual malnutrition present wounds frequently heal poorly and through and through steel wire sutures are employed. He feels that vagotomy needs more investigation before its acceptance as a valuable form of treatment.

## EDITORIAL

### CARDIOSPASM AND THE PROBLEM OF DISEASE CAUSATION

Walter C. Alvarez (1) to whom we are indebted for so many good and useful ideas, has always been careful to depict the effects of emotions upon gastrointestinal physiology, yet without exaggerating their importance. He is not, so far as I know, overly enthusiastic about modern, formalized "psychosomatics" and it is certain that he has refrained from adopting Freudian attitudes. Yet I know of no clinical psychologist more capable of divining the state of mind of his patient.

All this gives greater importance to his recent remarks with respect to the cause of cardiospasm. It is his opinion that the knot-like contraction of the distal esophagus which occurs in cardiospasm is an organic affair, and is due to a loss of the ganglion cells in Auerbach's plexus. He points out that in the slug, *Helix pomatia*, denervation of the rear half of the foot results in a permanent and firm contraction of the foot, which is the whole rear portion of the animal's body. Such lasting and tight contraction of smooth muscle, once it has lost its ganglion cells, is a very simple explanation of cardiospasm, and makes it superfluous to even consider fine-spun theories about the sympathetic and parasympathetic nerves. This idea applies equally to megacolon and whenever pathologists have carefully examined the distal and obstructing portions of the colon in this condition, they have found a practical absence of ganglion cells in Auerbach's plexus. This results in the permanent, knot-like contraction of the colonic segment. In some cases there may have been a congenital underdevelopment of the plexus, or the

1. Alvarez, Walter C.: A simple explanation for cardiospasm and Hirschsprung's disease. Gastroenterology, Nov. 1949, 13, 5, 422-9.

patient may have been subject to the neurotoxins of diphtheria or tetanus, or there may have been a sub-clinical and unrecognized attack of anterior poliomyelitis, resulting in the weakening or ablation of the plexus cells.

This conception of cardiospasm seems logical and probable. We have always wondered why there should be such atropine-defying contraction of smooth muscle in cardiospasm. It has also been a mystery why a metal dilator had to be used to undo something that the emotions had been supposed to cause. Alvarez admits that psychic disturbances have an influence in cardiospasm, but thinks that such disturbances obviously could not cause *all* the trouble. Emotional conflict must be a factor superimposed on an already existing organic lesion. Further than this Alvarez cautiously does not generalize, but actually his explanation of cardiospasm has important implications, for if accepted, it almost completely destroys the "psychosomatic" explanations of the disease, which, we must confess, have for some years stood as the *piece de resistance* of psychosomatic theory.

There is a current reaction in medical thought from the psychogenic conceptions of disease etiology. Even the primary psychoses which Freudian practice was powerless to influence, are now being increasingly viewed as manifestations of poorly-understood organic brain lesions. Terhune (2) advises fellow psychiatrists to practice "physiological psychiatry" and refers to many experiments and observations suggesting that mental disease rests on a purely physical basis.

The psychogenic theory of disease still is implanted in medical thought, but the present reaction favoring organic origins of disease is gaining momentum. The interesting nuances of modern psychiatric terms and

2. Terhune, W. B.: Physiological psychiatry. Am. J. Psychiatry, Oct., 1949, 106, 4, 241-249.

ideas have at times been wrongly employed,—by non-psychologists as a rule,—to clothe our ignorance of many disease processes. If new important physiological discoveries should eventually displace and defeat the psychogenic hypotheses of disease, then medicine would have evolved the most potent of arguments favoring materialism. It would not take too many broadsides such as that of Alvarez's to turn the trick.

Beaumont S. Cornell

"PREPYLORIC LOCAL GASTRITIS"

Haworth and Rawls (1) in carrying out upper gastrointestinal tract x-ray studies on 1289 patients, found evidence of what they call "prepyloric local gastritis" in 285 cases, which represents 22 percent of the total. They should be credited with advancing what appears, on first sight at least, to be a reasonable and brilliant explanation for the not-uncommon antral irregularities seen at fluoroscopy in patients with digestive complaints. These irregularities usually are discounted or, on the other hand, they may be mistaken as indicating cancer. Possibly gastroscopic studies ought to be carried out on a large number of such cases to determine if the appearance of the gastric mucosa also suggests (or confirms) the diagnosis of local gastritis. Until this has been done, some degree of hesitancy may persist in accepting this new entity, in spite of the fact that biopsies in nine of Haworth and Rawls' cases revealed lymphatic infiltration of the mucosa and definite edema of the submucous tissues.

It has long been known that gastritis frequently is associated with duodenal ulcer, and in the cases described, no fewer than 109 cases out of 285 were associated with this duodenal lesion. The chief value of this work is a possible new interpretation of an x-ray finding which has never previously been so definitely categorized. Reading the article at once brings up memories of prepyloric irregularities which were usually attributed to purely local spasm. The authors however go further and attempt to prove that these puzzling outline defects and blurring of the mucosal folds represent not only spasmodic contraction but a kind of inflammation, caused, in their opinion, by vagus influences. Thus it is logical to assume that prepyloric local gastritis may be a precursor of peptic ulcer. The condition responds well to ulcer regimes and usually disappears clinically and radiographically when sufficient treatment has been used. At times the filling defects produced by prepyloric local gastritis are sufficiently con-

stant as to suggest cancer, and this error has led to operations at which no malignancy was found, but in its stead, a simple edematous thickening of the antral wall. Until further critical reports, comparable in scope and penetration, with that of Haworth and Rawls, have appeared on this subject, there may remain some skepticism of accepting their new "roentgenographic disease" as fully established. In any case one should be on guard against a tendency to defer surgery in prepyloric gastritis in instances where cancer may actually be present.

1. Haworth J. B. and Rawls, N. B.: Prepyloric local gastritis. *Radiology*, 1949, 53, 720-728.

SCREEN TEST FOR CANCER

The article by Drs. N. Philip Norman and Anna M. Slicher on "A Practical and Inexpensive 'Screen Test' for Cancer" published in the February issue deserves attention on the part of the readers. There are a few additions, however, that should be mentioned to evaluate the test better. In my experience, their figure of accuracy of 97% positive is beyond that of what Bolen claims and that which occurred in my experience, where it was about 84%.

The questionable or borderline results are always a problem requiring checking for final decision. In the absence of pregnancy, endometriosis, and leukemia, which can be diagnosed clinically and the results of the test discounted, there are instances of inflammatory states (like ulcerative colitis, active tuberculosis, and acute and subacute infective disorders) in which the test may be confusing. Here, assistance is often gained by the careful observation of the spaces to note the presence of leukocytes which are generally attached to the erythrocytic masses. This has not been seen in the usual cancer case, although in one instance of colon cancer with abscess formation and another of generalized carcinomatosis with a low-grade peritonitis, the leukocytes were observed somewhat proving the infective type of result.

One must keep in mind that the test is not infallible, yet it is as useful as the other tests that have been advanced recently and very much more simple to carry out. In an occasional cancer case, the test may be so borderline that it is most confusing. Especially is this true in low-grade malignancy and prostatic carcinoma. It is a pleasure to add a few words to the article and especially to their excellent photomicrographs.

Anthony Bassler, M. D.

BOOK REVIEWS

MEDICAL MANAGEMENT OF GASTROINTESTINAL DISORDERS. Garnett Cheney, 478 pages. The Year Book Publishers, Inc., Chicago, 1950, \$6.75.

Cheney has written a valuable and very likable book. He approaches the broad subject of digestive disease from the standpoint of the internist and the general practitioner and succeeds in keeping his data simplified. Furthermore, he adopts a novel method of describing diagnosis and treatment under the headings of chief symptoms. Given a person with anorexia or with excessive appetite, he proceeds to outline what kind of examination should be made and what treatment ought to be used. One valuable feature is a careful selection of the few indispensable tests as opposed to the many which so often have chiefly an academic interest only. Unless the patient insists on a very elaborate "routine type" of examination, Cheney recommends doing only what is needed to make the

diagnosis. There are many hints gathered from the author's experience aimed at simplification, clarity and the comfort of the patient. References are not extensive and usually cite standard texts. It would be difficult to imagine a more satisfactory text for the average internist because it succeeds in consolidating both the theoretical and practical phases of gastroenterology into a workable scheme. We highly recommend it.

FUNDAMENTALS OF CHEMISTRY AND APPLICATIONS. Charlotte A. Francis, A. M. and Edna C. Morse, R. N., A. M., Ed. D. The MacMillan Company, New York, 1950, \$4.50.

This book is written especially for those who have had a short course in inorganic chemistry, as, for example in high school or in the first year of college, but who, because of the nature

of their work, need to understand something of organic and biochemistry as well. In such a category are nurses, dietitians and students of home economics. The book would also be valuable for a reading course for one who never had a course in chemistry but desired to understand the science. Finally it might well serve as a review for one attempting to refresh his memory of chemistry courses taken in past years. It is well written and very interesting.

GUIDE TO DIAGNOSIS OF OCCUPATIONAL DISEASES.  
Distributed by the Industrial Health Division, Dept.  
of National Health and Welfare, Ottawa, Canada.

One of the most useful sections of this book is a long list of occupations and their potential hazards. This is followed by a description of occupational diseases which may result from those hazards. There is an excellent chapter on the occupational dermatoses. Finally, the Workmen's Compensation Acts, as they apply in the various provinces of the Dominion, are discussed.

A STORY OF NUTRITIONAL RESEARCH (The effect of vitamin A and D and toxamines on bones and the nervous system) Sir Edward Mellanby, K. B. E., F. R. S. Williams and Wilkins Company, Baltimore, 1950, \$5.00.

This text of 453 pages represents a scientific autobiography of the author whose researches form a basic part of the present science of nutrition. It is divided into two parts,— Vitamin A deficiency and incoordination of movement, and The anticalcifying effect of cereals. In 1913 Mellanby was requested by the Medical Research Committee (later the Medical Research Council) to study rickets particularly from the stand point of the part which oxidation processes might play in the etiology. It was soon found that rickets was due to a deficiency of a fat soluble vitamin which at first was thought to be vitamin A. It was also noted that the use of cereals hastened the

development of rickets in those animals which were on a diet deficient in the fat soluble vitamin. Eventually the fat-soluble vitamin was found to be a mixture of A and D, but it was not till 1924 that vitamin D2 was separated from vitamin A. Mellanby not only recognized that incoordination of movement due to nerve degeneration occurred in vitamin A deficiency but that nerve degeneration resulted from bone dysplasia from the same cause. He emphasizes the rachitogenic action of cereals due to their phytic acid content. He thinks that the extreme degrees of osteomalacia seen in China are caused by the heavy phytate content of the cereal diets and are not due simply to absence of vitamin D.

METABOLISM AND FUNCTION. Edited by D. Nachmansohn, M. D., 348 pages. Elsevier Publishing Co., Inc., 215 Fourth Ave., New York 3, N. Y., 1950, \$7.00.

Nachmansohn has edited an unusually interesting collection of contributions from many physiologists and biochemists, which together form an anniversary volume in honor of the distinguished German physiologist, Otto Meyerhoff, on the occasion of his 65th birthday. Meyerhoff now holds the position of Research Professor of Physiological Chemistry in the School of Medicine of the University of Pennsylvania. The articles deal with the chemical changes taking place within muscles and nerves during their physiological activity, many being written by former pupils and associates of Meyerhoff. The leading article by A. V. Hill may be said to summarize the fluctuations which have occurred in our conceptions of the chemistry of muscular and neural function. Lactic acid, as the center of interest, shifted to phosphagen, and now adenosinetriphosphate has largely eclipsed the others. A few of the articles are in German and French. The book should be obtained by those desiring to be brought up to date on muscle and nerve biochemistry, but it should be borne in mind that it is not easy reading for anyone except an experimental biochemist.

## GENERAL ABSTRACTS OF CURRENT LITERATURE

MELCHIOR E. (Basel, Switzerland). *Emetin und appendicitis. (Emetine and appendicitis.)* Hely. Chir. Acta; 1949; vol. 16, no. 2; 126-149.

The good results of emetine injections in the treatment of gallbladder infections encouraged M. to use this drug in cases of complicated appendicitis, acute purulent peritonitis or thrombophlebitis of appendicular origin, as a help to the operation.

When the surgery alone was helpless, emetine brought forth an amelioration, in the dose of 0.03-0.05 gm. twice daily with a maximum of 1 gramme for a cure.

M. Demole (Geneva).

ROULET, F. (Basel, Switzerland). *Weitere Versuche über experimentelle Magengeschwüre und deren Behandlung. (New researches on experimental peptic ulcer and its treatment.)* Schweiz. med. Wschr.; 20 Aug., 1949; vol. 79, No. 33; 749-750.

By injecting histamine at the same time as a synthetic anti-histamine drug, R. produces without shock a peptic ulcer in 80 percent of the guinea pigs. These animals were then treated during 2½ weeks with Robuden, an extract of stomach mucous membrane. From 18 guinea pigs, 7 showed a "tendency to heal," and 3 of them scars of their ulcers, whilst this occurred only once to animals that had not been treated; 3 guinea pigs were uninfluenced by Robuden and one had a recurrence of peptic ulcer.

M. Demole (Geneva).

BRIGGS, I. A.: *The treatment of congenital atresia of the esophagus with tracheo-esophageal fistula.* Annals of Surgery, May 1949, Vol. 129, No. 5, 572-587.

Congenital atresia of the esophagus was first discovered by Gibson in 1703. From that time till 1918 very few cases were reported in the literature. This condition is not unusual since it is estimated to occur once in every 2500 births. The variations of this anomaly are important to the surgeon because the type of operation, as well as the approach, depends on the nature of the lesion. The diagnosis is made relatively easily on the history of excessive drooling of

saliva and the immediate regurgitation of everything given by mouth, together with stridor. Barium should not be given orally to make this diagnosis because it may enter the tracheobronchial tree and produce serious pulmonary difficulties. Lipiodol should be used instead. A large amount of air in the intestinal tract would point to a tracheo-esophageal fistula.

The treatment of congenital atresia of the esophagus has been unsuccessful in the past. End to end suture of the esophageal segments with closure of the tracheal fistula is the ideal procedure, and can be done through a right extra pleural approach. If the segments are too far apart to be anastomosed, an esophago-gastric anastomosis can be done with the stomach being brought into the left chest. This can be done surprisingly easily in these young infants. The author believes that preliminary gastrostomy is useful if positive intra-tracheal anaesthesia is to be used or if much air-distension is present. Eleven cases were operated upon from 1941 to 1948 of whom one is alive and well. In the past year seven such patients were operated upon in all of whom gastrostomy was done as a preliminary procedure. All seven of these have recovered. This is undoubtedly also due to the use of both penicillin and streptomycin for the prevention and control of infection.

Philip Ladin.

HARRINGTON, STUART W.: *The surgical treatment of pulsion diverticula of the thoracic esophagus.* Annals of Surgery, May 1949, Vol. 129, No. 5, 606-618.

Pulsion diverticula are usually false in that only mucous membrane is concerned in the herniation. They are due to a congenital defect in the muscle of the esophagus, through which the mucous membrane is forced. The most common location is in the pharyngoesophageal junction. The next most common site is in the lower third of the esophagus. The frequency of the lower esophageal point can be estimated by the fact that the author treated surgically 216 patients with pharyngoesophageal diverticula during the same period in which he treated eight patients with pulsion diverticula of the esophagus. Pulsion diverticula usually occur in the

right posterior wall of the esophagus three to four inches above the cardia and extend into the right thoracic cavity. Eight cases are reported in this paper with an average age of 52 years.

The symptoms of these diverticula are: the sensation of food sticking in the throat often in association with low substernal pain. As the diverticulum increases in size it causes progressive dysphagia, choking attacks and regurgitation or vomiting of food soon after its ingestion. Food that was taken one day before may be regurgitated. Inflammation and ulceration may be caused by the retained food and secretion, and this may be followed by perforation into the lung or mediastinum. X-ray and esophagoscopy are used in making the diagnosis and also in planning the operation. Pre-operative treatment requires in addition to the usual procedures, careful emptying of the diverticulum and at least one dilatation of the esophagus below the diverticulum. The operation consists of excision of the diverticulum with a repair of the esophageal musculature. One leaf of the pleura may be sown over the suture line while the other is left open for drainage. Seven of the eight patients reported recovered from the operation and have been relieved of their symptoms. However, three of these continued to have some attacks of esophageal spasms.

Philip Ladin.

WEST, J. P.: *Total gastrectomy for carcinoma of the stomach.* Annals of Surgery. Vol. 129: No. 3 (Mar.) 1949.

This paper reports a study of 11 cases who survived total gastrectomy out of a total of 18 cases. Six of the patients who survived are now dead. The author emphasizes the nutritional difficulties following total gastrectomy and is in accord with the belief that a small portion of the distal end of the stomach should be preserved whenever possible, inasmuch as it appears to make subsequent feeding more effective. The writer believes that some deaths reported as due to recurrence of carcinoma might actually be due to inanition. He reports such a case with autopsy finding of extreme starvation.

Philip Ladin.

MAYFIELD, L. H. AND WAUGH, J. M.: *Sigmoido-cutaneous fistula resulting from diverticulitis of the sigmoid colon.* Annals of Surgery. 129: (Feb.) 1949.

The authors review 17 cases of sigmoido-cutaneous fistula which were seen at the Mayo Clinic. These were the remaining group after discarding the cases that could not be followed up. The authors point out that cutaneous fistulae from sigmoidal diverticulitis have a significant incidence in spite of the absence of many reports. The bladder is the more common site for fistula formation, but the incidence of sigmoido-cutaneous fistula varies in different series from 3.2% to 18.4%. These cases generally follow incision and drainage for an abscess due to perforation of a sigmoidal diverticulum. The literature has emphasized the tendency for these fistulae to heal spontaneously but it is recommended that about one year be allowed for the healing to occur before the surgical correction is employed. The mode of formation of the fistula is supposed to be as follows: adherence to the abdominal wall, abscess formation, and opening of the abscess through the skin either spontaneously or by incision and drainage. The symptoms of these fistulae are as expected, with abdominal pain, chills, and fever occurring when the fistula closes over, and reoccurring when it drains. None of these could be seen on sigmoidoscopy. X-ray examination of the colon was the most important aid in diagnosis and differential diagnosis.

Philip Ladin.

POTH, EDGAR J.: *Bowel healing as influenced by intestinal antiseptics.* Southern Med. Jour., v. 41, p. 672, 1948.

Using dogs as experimental animals, experiments were performed to study the minute process of healing following anastomosis of the colon. Both open and closed techniques of anastomosis were studied. In the control experiments, wound infection, peritonitis, stitch abscesses, and local soft tissue infections were the usual findings. In those instances where adequate treatment with sulfasuxidine and sulfathalidine was given, evidence of infection was seldom encountered. There was minimal edema of the mucosa in the treated animals in contradistinction to extensive edema in the controls.

Microscopically, the control specimens showed acute inflammation characterized by extensive edema, prolonged leukocytic infiltration, and delayed revascularization and fibroplasia. The specimens from the treated cases exhibited slight inflammation which subsided rapidly and was characterized by moderate edema, limited leukocytic infiltration, and rapid revascularization and orderly fibroplasia. Addition of streptomycin to the sulfonamide therapy did not alter the healing process materially.

G. F. Gain  
Courtesy Biological Abstracts.

FRASER, R. W. AND WEST, J. P.: *Management of bleeding duodenal ulcers.* Annals of Surgery. Vol. 129: no. 3 (Mar.) 1949.

The authors present a study of 177 consecutive patients with severe bleeding from duodenal ulcers. 165 patients were treated by non-operative methods with a mortality of 4.2% and 12 patients were treated by operation with a mortality of 33.3%. There were 84 patients over 50 years of age with a total mortality of 9.5% as compared with 93 patients under 50 with a mortality of 3.2%. It is interesting to note that of 84 patients under 50 years of age treated by non-operative methods, there was no mortality. The authors feel that the occasional indications for surgical treatment of bleeding duodenal ulcers are limited with few exceptions to patients over 50 years of age.

Philip Ladin.

PORTER, H. W. AND CLEMAN, Z. B.: *A preliminary report on the advantage of a small stoma in partial gastrectomy for ulcer.* Annals of Surgery. Vol. 128 Pgs. 417-428 (Apr.) 1949.

Although the results of partial gastrectomy for chronic peptic ulcer have been satisfactory there is no doubt the patient is often left with other disabilities. The authors feel that many of these can be eliminated by a minor change in the type of operation carried out. The major cause for post-operative symptoms is believed to be excessively rapid emptying of the remaining stoma ("dumping syndrome") with the result in bulging of the jejunum. The authors emphasize the quantitative emptying time, rather than the total emptying time and point out that a sphincteric-like action can be obtained at the gastro-jejunum stoma by making a small opening (Hofmeister). 118 sub-total gastrectomies for ulcer are reported utilizing a stoma 2.5 Cm. in length. The advantages listed are:

1. decreased incidence of leakage at the upper end of the anastomosis.
2. decrease in retrograde influx into the proximal jejunal loop.
3. prevention of bulging of the jejunum after the intake of food.
4. diminished risk of post-operative hemorrhage.
5. increased emptying time and sphincteric-like action of the stoma.

In 90 cases of this series followed up radiologically there was no jejunal bulge in 84 cases and slight jejunal bulge in 6. With a small stoma the average emptying time was 58 minutes. The symptoms of ("dumping") syndrome were present in only five patients three months post-operative, utilizing the small stoma, and only two of these persisted. The authors report one case of severe dumping syndrome which was completely relieved by revising the previous operation and reducing the size of the stoma to 2 1/2 Cm. Earlier feeding is also possible with this type of operation thereby shortening convalescence.

Philip Ladin.

WILBUR, DWIGHT L. AND WATTS, MALCOLM, S. M.: *Peptic ulcer. Modern criteria for diagnosis and attempted diagnosis of healing.* Radiology 52:6,800, June 1949.

The clinical diagnosis of peptic ulcer depends upon the history given by the patient. The so-called "typical history" is present and diagnostically accurate in 80 to 90% of all cases. In others there may be an "atypical" story, the symptoms may be due to complications, or there may be pain or vomiting of the crisis type. Radiologic diagnosis, which is said to be 95% accurate, depends largely on demonstration of a gastric or duodenal niche or constant deformity of the duodenum. When there is a discrepancy between the clinical and radiological findings the clinician will be influenced in his diagnosis by such factors as 1)

the character of the patient's complaints and their resemblance to the symptoms of ulcer; 2) the certainty of his clinical impression of ulcer; 3) his past experience as to the accuracy of reports from the radiologist who examined the patient; 4) the presence of other evidence of organic disease; 5) the results of subsequent clinical and radiologic observations of the patient.

There is no satisfactory clinical evidence of healing of an ulcer. Persistence of symptoms means activity of the lesion, but the reverse does not hold. Radiologic evidence for healing is unsatisfactory also though disappearance of the niche and the occasional return of the duodenal bulb to normal probably indicate healing.

Among the interesting but inconclusive findings were that the radiologist made the diagnosis of gastric and duodenal ulcer more frequently than the clinician was willing to accept it, that when the radiologist reported irritability or inflammatory change in the stomach or duodenum, a diagnosis of ulcer was not made clinically in a single instance, and that when a clinical history typical of ulcer was present the radiologist made a diagnosis of gastric or duodenal ulcer in 28 of 41 cases and reported findings of a normal stomach and duodenum in only three.

Franz J. Lust.

STEVENSON, G. A. AND YATES, C. W.: Accuracy of roentgen diagnosis of benign gastric ulcer. *Rad.* 52,633. May 1949.

The experienced radiologist is able to be highly accurate in the diagnosis of benign gastric ulcer. In a series of 91 adequately followed gastric ulcer patients, the roentgenological report of a benign lesion was accurate in 93.4%. In spite of various criteria for the differential diagnosis between benign gastric ulcer and gastric carcinoma, we are unable, on reviewing the roentgenograms and the fluoroscopic findings, to find any difference in the six malignant cases erroneously diagnosed as benign ulcers in this series. We believe, therefore, that it is impossible, at any one roentgenological examination, to definitely differentiate a gastric ulcer from a gastric carcinoma. No particular fault can be found from a roentgenologic standpoint with either the medical or surgical procedures needed to enhance the accuracy of the roentgenologic diagnosis. However, since gastric carcinoma implies a very poor prognosis, it may be wise to consider seriously immediate surgery for all cases of roentgenologically diagnosed benign gastric ulcer, in the hope of early removal of the carcinoma in the approximately 10% of cases in which the diagnosis is wrong.

Franz J. Lust.

ADLERBERG, DAVID AND HAMMERSCHLAG, ERNEST: The postgastrectomy syndrome. *Surgery* 21,5,720. May 1947.

A group of fourteen patients, who for many years after partial gastrectomy for ulcer had been unable to gain weight and presented difficult nutritional problems, have been investigated. The symptoms were analyzed and divided in two groups: early and late postprandial symptoms. The early symptoms were caused by mechanical factors, small stomach and rapid emptying, and overloading of the small intestine. The late symptoms were due to chemical factors, hypoglycemia secondary to the exaggerated postprandial hyperglycemia, and occasionally secondary to disturbed intestinal absorption. The postgastrectomy syndrome was caused by a sequence of these early mechanical and late chemical factors, exaggerated by distinct psychoneurotic stigmas. Many of these individuals were stomach constrictors. The shock of the operation, the postoperative course, later the postgastrectomy syndrome, and finally the diminished physical and mental resistance associated with underweight and malnutrition exaggerated the stomach awareness. The ultimate effect was a conflict between the postprandial symptoms, the late manifestations of which are relieved by food, and the fear to eat. The treatment of these patients presents a series of difficult clinical, nutritional and psychological problems, all of which require consideration.

Franz J. Lust.

FUREY, WARREN W.: X-ray observations before and after vagotomy. *Radiology* 51,6,806. December 1948.

The radiologist should be familiar with the vagotomy controversy and with the pertinent clinical and laboratory findings and thus know what to expect when asked to study one of these patients. Furey demonstrates some of the

occasionally startling and paradoxical roentgen findings. It is rather striking to have a patient appear well, state that he feels fine, has no distress, eats everything, sleeps well and has gained weight since operation, and then to find that his stomach is markedly distended, containing considerable quantities of retained food material and retaining opaque material almost completely, in some instances over a 24 hour period; to have great difficulty in visualizing the duodenal bulb and, when it is demonstrated, to observe a marked deformity; sometimes to find evidence of a persisting ulcer crater in the complete absence of pain or tenderness on direct palpation.

Franz J. Lust.

CAMPBELL, B. A. AND BURTON, A. C.: Stratification of bile in the gallbladder and cholelithiasis. *Surg. Gyn. Obstetr.* 88, 6, 731-738.

The bile of cats, cattle and human beings has been investigated for the evidence of stratification as observed roentgenologically.

The observations made suggest that stratification occurs as a normal physiological phenomenon in the functioning Gallbladder. Incomplete emptying of the Gallbladder is the most likely cause. Gallstones floating between two strata are demonstrated in Roentgenograms. In 65 Gallbladders of normal cattle 60 per cent showed an increase in specific gravity from top to bottom of .005 to .023 units.

Diffusion does not suffice to mix the separate strata.

Persistent stratification may favor the precipitation of cholesterol stones.

MACMAHON, H. E. AND THANNHAUSER, S. J.: Xanthomatous Biliary Cirrhosis (A Clinical Syndrome). *Ann. of Int. Med.*, Jan. 1949, Vol. 30, No. 1, 121-179.

Evidence of skin xanthoma with chronic jaundice and liver disease in relatively rare cases was recognized for the first time by Addison and Gull in 1851, and has been recorded in the literature throughout the years by various authors. Thannhauser and Magendantz in 1937 and Thannhauser in 1940 described as "xanthomatous biliary cirrhosis" a typical clinical syndrome characterized by the following features: (1) Skin xanthoma, (2) enlarged liver and spleen, (3) obstructive type of jaundice of years' duration, (4) extremely high values for total cholesterol as well as for lecithin, (5) the serum is transparent and not emulsion dense hyperlipidemia. The present paper deals with detailed clinical histories and laboratory findings of five cases observed over a long period, three autopsies and four biopsies taken at an early stage of the disease. The authors arrive at the following conclusions.

The marked accumulation of cholesterol and lecithin at the beginning of the disease is probably not only the result of a retention of bile but also the consequence of increased production of the two lipoids. The diagnosis of xanthomatous biliary cirrhosis should be made only if all five signs are present. In biliary cirrhosis neither skin xanthoma nor hyperlipidemia are found. Nor are they found in acute or chronic hepatitis. The only other disease having similar symptomatology is hemochromatosis. The latter, however, occurs mainly in males while xanthomatous biliary cirrhosis has so far been reported, with one exception, only in females. Furthermore, in xanthomatous biliary cirrhosis the hyperlipidemia appears at the very beginning of the disease while in hemochromatosis it appears in its last stages. Therapy: The patient should become a vegetarian since humans do not usually absorb vegetable sterols. Animal protein should be given only in the form of skimmed milk, egg white or cottage cheese. All animal fats and meat should be avoided. Intramuscular injections of all vitamins should be given twice weekly. The therapeutic value of this diet is limited as it excludes only the exogenous quota of animal cholesterol whereas the endogenous hyperproduction which is probably the cause of the disease continues unabated. Choline and methionine and other lipotropic substances are not of great value in this disease as neither increased fat transport nor a fatty liver are present.

Xanthomatous biliary cirrhosis should not be classified as formerly suggested under the group of essential xanthomatosis of the hypercholesterolemic type, it is a liver disorder and a disease entity in its own right.

Walter Cane.

AMER. JOUR. DIG. DIS.

ROOST-PAULI, M. AND ROOST-PAULI, H.: *Resorption and destruction of streptomycin in the large bowel.* Schweiz. Med. Wschr. 1949, 9, 39, 942-944.

After rectal injection of 1 gm. of streptomycin in 500 cc. of water no streptomycin can be detected in the blood during the next 6 hours. The drug is sometimes excreted in the urine but never more than 8.87 per cent. From 6.4 to 62.2 percent of the streptomycin which has been introduced into the rectum can still be found in the colon 7 hours later. Experiments *in vitro* have shown that the stools are capable of destroying up to 74 per cent of streptomycin in 6 hours. M. Demole, Geneva.

GRACE, W. J., SETON, P. H., WOLF, STEWART AND WOLFF, HAROLD G.: *Studies of the Human Colon: I. Variations in Concentration of Lysozyme with Life Situation and Emotional State.* The Am. J. of the Med. Sc., March, 1949, Vol. 217, No. 3, 241-251.

Any piece of research and publication in which Wolf and Wolff take part can be depended upon to be logical in presenting the questions to be answered, painstakingly systematic in answering them, of interest to general practitioners and specialists alike and always leaving behind a new visual field of insight into the complicated mechanism of psychosomatic medicine. The present paper is no exception to this rule.

Lysozyme, a bacteriolytic and mucolytic enzyme, was first described by Sir Alexander Fleming in 1922, when he was studying the antibacterial properties of tears. Since then the enzyme has been shown to be present not only in human tears but also in nasal mucus, gastric juice, the secretions of the large and small intestines and in human milk. All pathological transudates and exudates contain large amounts. The richest source of this lytic enzyme is egg white of hen's eggs. Meyer and his associates have shown that lysozyme concentrations are very high in the gastric juice of patients with peptic ulcer and in the stools of patients with chronic ulcerative colitis. Meyer et al. have demonstrated that lysozyme will digest mucus and postulate that the destruction of the protective coating of the bowel exposes the underlying mucosa to the action of noxious agents of the intestine such as hydrochloric acid or the indigenous bacterial flora. These postulates they have substantiated in part by feeding lysozyme to dogs and thus producing acute ulceration of the upper gastro-intestinal tract.

Many doubts have been raised as to the clinical significance of high lysozyme concentrations, and opinions have even been uttered that lysozyme is the product, not the cause, of ulceration. These questions were made the subject of the present study by the authors. They arrived at the following conclusions.

(1) In normal subjects a rise in colonic lysozyme concentrations from 0.4 to 10.8 units per gram may occur in response to situational threats productive of anxiety and apprehension.

(2) Patients with ulcerative colitis in a state of remission showed lysozyme concentrations of 0.7 to 1.6 units per gm., those with mild symptoms showed concentrations of 13-25 units per gm., with moderately severe symptoms 40 to 100 units. Sustained marked elevation usually preceded a period of bloody diarrhea.

(3) In patients with mucous colitis lysozyme concentration was low (0.4 to 1.5 units per gm.).

(4) The possibility that ulceration itself might provoke elevation of the lysozyme level was investigated by analyzing the stools of a subject with ulcerated carcinoma of the colon. Lysozyme concentration, however, was persistently low (3.2 units per gm.).

(5) Attempts to assess the effects of lysozyme applied to the intact colonic mucosa were made on a patient who was healthy except for a colostomy through which had evantered a large segment of sigmoid colon. Human tears containing lysozyme in a concentration of 600 units per gram were applied to the surface of the bowel and allowed to remain there for 24 hours. In three of four such experiments a small, sharply circumscribed area of inflammation and edema was noted at the point of application. Control applications of normal saline, boiled tears and dry cotton failed each time to produce any lesion.

The authors conclude from these data that lysozyme concentration in bowel secretions is highly relevant to the occurrence of ulceration.

Walter Cane.

MAY, 1950

RICHMAN, ALEXANDER AND COLE, RALPH: *Subtotal gastrectomy in the treatment of chronic recurrent pancreatitis.* J. Mount Sinai Hospital New York, 15, 3, 132, Sept. 1949.

The authors present a case of a recurrent pancreatitis of 14 years' duration in which the diagnosis was established by clinical, laboratory and operative findings. Following the development of a gastric ulcer, subtotal gastrectomy was done to remove the lesion and alleviate the pancreatitis by interference with the secretin mechanism of pancreatic secretion. A dramatic cure resulted with disappearance of pain, steatorrhea, and crætorrhea. Gain in weight and strength were sufficient to permit the patient to return to work after 8 years of disability.

Alleviation of the pancreatitis can be explained by the interference with the secretin mechanism of pancreatic secretion which resulted from diminution in acid output and diversion of the acid chyme from the duodenal mucosa into the jejunum. The reduced quantity of secretin is responsible for formation of a lessened amount of pancreatic juice which flows under decreased pressure through pancreatic ducts which have been constricted and partially blocked by calcification and cicatrization. Thus, distention of the ducts does not occur and pain is not experienced. Since the diminished quantity of pancreatic juice has free access to the intestine, digestion and absorption of food are carried on more efficiently than when there is obstruction to the flow.

Franz J. Lust.

HAWORTH, JAMES B., AND RAWLS, NOEL B.: *Prepyloric local gastritis.* Radiology 53, 5, 720, November 1949.

Prepyloric local gastritis is a disorder manifested by post-prandial epigastric distress and radiologic abnormalities of the distal segments of the stomach. The criteria of this condition as seen during the roentgenological examination are a) the presence of an initial gastric fluid residue (hypersecretion), b) visible prepyloric mucosal deformity, c) localized prepyloric tenderness on deep pressure, d) spasm along the distal portion of the lesser curvature, with or without pylorospasm, e) interference with normal peristalsis and antral systole. The characteristics of the deformed prepyloric mucosal folds can be manifold. There is almost invariably a thickening of the individual folds, with varying degrees of distortion of the pattern which they form, especially along the lesser curvature. The authors believe prepyloric local gastritis to be a precursor of gastric and duodenal peptic ulcer in many instances.

Franz J. Lust.

LORD, JERE W. JR., HOWES, EDWARD L., AND JOLLIFFE, NORMAN: *The surgical management of chronic recurrent intestinal obstruction due to adhesions.* Ann. of Surg. 129, 3, 315, March 1949.

The authors report three cases who showed a remarkable absence of any symptoms or signs of intestinal difficulty following the Noble plication procedure in contrast to the continuous ill health for months and years prior to plication. The authors, therefore, believe that the results obtained with this operation deserve wider recognition and that the technique will find increasing acceptance among surgeons who are called upon to operate for intestinal obstruction due to adhesions. As Noble has stated, it places the surgeon in control of the formation of adhesions instead of allowing them to form by chance with the possibility of obstruction due to kinking and angulation. Plication of the small intestine is not technically a difficult procedure, and requires only a short time to complete after all the adherent loops have been freed and adhesions divided, but the separation of the adhesions is a long painstaking procedure. Normal function of the small intestine is promptly restored by the operation and the ingestion and absorption of proper nutrients follows, causing the patients to gain weight and lose manifestations of their deficiencies. Two of three patients became free of morphine addiction after operation.

Franz J. Lust.

FRASER, ROBERT W., AND WEST, JOHN P.: *The management of bleeding duodenal ulcers.* Ann. Surg. 129, 3, 290, March 1949.

The total mortality in a group of 177 consecutive patients suffering moderate to severe hemorrhage, from duodenal ulcer, was 6.2%. The nonoperative treatment of 165 patients resulted in 7 deaths, a mortality of 4.2%. Operative treatment of 12 patients suffering from severe and uncontrolled

hemorrhage was followed by 4 deaths, a mortality of 33.3%. The operation apparently saved the lives of four patients in this series but at the same time it appears probable that some of the patients subjected to operation might have survived without surgical intervention. The occasional indications for surgical treatment of bleeding duodenal ulcer are limited with few exceptions to patients over 50 years of age.

Franz J. Lust.

SAPPINGTON, THOMAS S., AND BOCKUS, HENRY L.: Nitrogen metabolism in chronic idiopathic ulcerative colitis and its therapeutic significance. *Ann. of Int. Med.*, August 1949, Vol. 31, No. 2, pg. 282-302.

The authors have undertaken a preliminary study of the protein requirement of patients suffering from chronic idiopathic ulcerative colitis. In their opinion it would seem reasonable to suppose that many patients afflicted with this disease are deficient in protein. The disease might be expected to cause an increase in the excretion of fecal nitrogen and at the same time a decrease in protein intake due to anorexia, nausea and vomiting. If such a protein deficiency existed, commonly in these patients, at alone, the authors reasoned, might be sufficient cause for the failure of the lesions to heal.

Each of five individuals studied was found to be deficient in protein as indicated by the presence of a positive nitrogen balance. It was assumed that in general the normal adult individual does not store protein and that, under conditions of constant adequate nitrogen intake and cardiorenal competency, the nitrogen excretion is equal to the nitrogen intake; and it was further assumed that, under these same conditions, a positive nitrogen balance was evidence of pre-existing protein deficiency. The existence of protein deficiency cannot be excluded by the absence of physical signs of malnutrition or by the presence of a normal concentration of serum protein.

The authors observed that on all occasions positive nitrogen balance either preceded, or coincided with, clinical improvement. No clinical improvement was observed during any period of negative balance. In their opinion it is possible that the demonstration of consistent positive nitrogen balance (in the absence of azotemia) may enable the clinician to predict clinical improvement in a patient critically ill with colitis, or at least to be assured that the metabolic stage is set for remission of the disease. In four instances positive nitrogen balance preceded clinical signs of improvement by several weeks. Follow-up studies on two of these patients and another to be reported elsewhere indicated that high protein feeding for several months may be necessary to correct the protein deficit in these patients. Positive nitrogen balance could be achieved and maintained in these patients by giving diets moderately high in protein with or without the parenteral administration of protein hydrolysates or blood. Parenterally administered protein hydrolysate was relatively well utilized, but orally given protein was more effective.

The authors do not claim that chronic idiopathic ulcerative colitis is primarily a manifestation of protein deficiency, and no attempt was made to compare the therapeutic efficiency of high protein administration with the other generally accepted forms of treatment. In their opinion it is probable that all of these measures may be important in bringing about a remission. They emphasize, however, the prevalence of protein deficiency in these patients. They point out that positive protein balance may be necessary (though doubtless not sufficient) for achieving clinical remission. They suggest that the period of time required for complete restoration of tissue protein may be quite lengthy, and that a partially corrected unrecognized chronic protein deficiency may be a very important factor in permitting relapse of the disease.

Walter Cane.

SAPPINGTON, THOMAS S., AND BOCKUS, HENRY L.: Nitrogen balance studies in chronic peptic ulcer disease. *Ann. of Int. Med.*, August, 1949, Vol. 31, No. 2, pg. 271-281.

The authors have noticed that considerable interest has been shown in recent years in the nutritional aspects of peptic ulcer therapy. This interest was among others, expressed in the "hyperalimentation" treatment by Co Tui which emphasized the beneficial effect of a diet containing very large amounts of partially hydrolyzed protein.

As there are ample data to demonstrate the importance of a high protein intake in the treatment of a host of chronic diseases, the authors decided to study the protein requirement in patients with chronic peptic ulcer.

The protein requirement of five patients with chronic peptic ulcer was studied by means of nitrogen balance surveys as well as the more routine chemical analyses. Two of these patients gave evidence of previous nitrogen deficiency and hence an increased requirement of protein; another patient was "probably" in a similar state; a fourth patient was "probably not suffering from protein deficiency;" the fifth patient had no demonstrable protein deficit.

The authors call attention to the fact that in all five patients satisfactory relief of symptoms and ulcer healing took place despite a deficiency in the diets of some of the patients.

The authors advocate the administration of a moderate surplus of protein to chronic ulcer patients, and they feel that it is not necessary to prescribe excessive amounts of protein for patients in moderate nitrogen deficit in order to accomplish ulcer healing. Fifteen grams of nitrogen or 95 gm. of protein are suggested as a minimum daily intake for patients in this group. If the diet is to be restricted to milk, a food substance rich in whole protein (e. g., calcium caseinate or skim milk powder) should be added to meet this requirement. The authors conclude their article with the statement that "the oral administration of protein hydrolysates would seem to offer no advantage over whole protein in these patients."

Walter Cane.

MILHAUD, G., DEMOLE, M. AND EPINEY, J.: *Recherches on the "cathepsin" of gastric juice.* *Helv. Med. Acta*, 1949, 16, no. 3/4, 244-247.

A new proteolytic ferment was described in 1940 by Freudenberg of Basel, obtained from the gastric juice of the new-born, and capable of digesting protein at pH 3.3 as contrasted with pH 2.2 for pepsin. The authors studied this cathepsin in 78 adults employing the measuring technique of Buchs. In healthy persons the enzymatic power of cathepsin and of pepsin are equal. In achlorhydria, the catheptic power often is lacking and is always less than the peptic power. In gastritis, even in cases where the acidity is low, the catheptic power invariably is high. Ulcer patients show a high digestive capacity for both ferments, and it is only in ulcer patients that the cathepsin is frequently higher than the pepsin.

M. Demole, Geneva.

DELLA SANTA, R. ET V. KAULLA, K. N. (Geneva Switzerland). *L'hypoprothrombinémie provoque chez les hépatiques. (Artificially created hypoprothrombinæmia as a test for hepatic function).* *(Helv. med. Acta*; Sept. 1949; vol. 16, No. 3/4; 251-257).

The tolerance test with vitamin K, imagined by F. Koller (Zurich) is one of the best tests for hepatic function, if the plasmatic prothrombin is low, but it cannot be used with normal prothrombinæmia.

Having ascertained that a small dose (50 mgm.) of Dicumarol in patients with liver diseases resulted in a persistent hypo prothrombinæmia during a few days (instead of returning to normal conditions in 24 hours) v.K. suggested to use it as an hepatic test.

D. S. and v.K. describe here their method, using a much better tolerated drug, *Tramezan*. The test is positive when the former prothrombinæmia is not recovered 48 hours later, after a unique quantity of 300-450 mgm. is administered.

M. Demole (Geneva)

ODIER, J. AND MACH, R. S. (Geneva, Switzerland). *Le volume du liquide extra-cellulaire chez les obèses. (The volume of extra-cellular fluids in obese patients).* *(Praxis; 22. Sept. 1949; vol. 38, No. 38; 834-838).*

Using the test with Natrium sulfocyanid, O. and M. have ascertained that the volume of extra-cellular fluids is much smaller in obese patients (20.1% of the body weight) than in normal people (26.4%).

But if an obese person is thought to be relatively less hydrated than a normal one, is it really the case, i.e. do his extra-cellular spaces contain less water? Comparing now the extra-cellular fluids to their ideal weight (instead of their actual weight), O. and M. found out that in cases of slight obesity the percentage of extra-cellular fluid is normal, and superior to normal in case of large obesity.

M. Demole (Geneva).

## THE AMERICAN CONGRESS OF PHYSICAL MEDICINE

Will hold its twenty-eighth annual scientific and clinical session August 28, 29, 30, 31 and September 1, 1950 inclusive, at the Hotel Statler, Boston, Massachusetts. Scientific and clinical sessions will be given on the days of August 28, 29, 30, 31 and September 1, 1950. All sessions will be open to members of the medical profession in good standing with the American Medical Association. In addition to the scientific sessions, the annual instruction seminars will be held August 28, 29, 30, 31. These seminars will be offered in two groups. One set of ten lectures will consist of basic subjects and attendance will be limited to physicians. One set of ten lectures will be more general in character and will be open to physicians as well as to therapists, who are registered with the American Registry of Physical Therapy Technicians or the American Occupational Therapy Association. Full information may be obtained by writing to the American Congress of Physical Medicine, 30 North Michigan Avenue, Chicago 2, Illinois.

### AMERICAN CAN CO. RE- PORTS NET OF \$10.02 A SHARE

In a preliminary report pending completion of its statement to stockholders, American Can Company today placed its 1949 earnings, after taxes, at \$27,683,690, which is equivalent after provision for dividends on preferred stock, to \$10.02 per share of common. Earnings in 1948 were \$26,910,269 or \$9.71 per share of common.

The 1949 earnings figure is after a charge against earnings of \$1,440,105 for translation of net assets in Canada into United States dollars following Canadian devaluation.

Net sales in 1949 totaled \$468,390,818 compared with \$409,511,398 in 1948, a gain of 14 percent, about two-thirds of which was due to price increases at the outset of 1949 to cover the exact rise in costs of tinplate and labor differentials as provided in customer contracts.

The ratio of net earnings to sales was 5.9 per cent, compared with 6.6 per cent in 1948.

The company's annual report was issued early in March.

## TWO DRUGS JOINED TO COMBAT COLDS AND NASAL ALLERGIES

Combination of a new antihistaminic with a highly effective nasal decongestant to combat colds and nasal allergies was announced by Winthrop-Stearns Inc.

Called Neo-Synephrine Thenfadiol hydrochloride, the solution is available on prescription.

The combination marks the first commercial preparation of Thenfadiol, the recently developed antihistaminic which has proved successful in two and a half years of clinical investigation in the treatment of allergies.

Neo-Synephrine Thenfadiol solution contains 0.25 per cent of Neo-Synephrine hydrochloride and 0.1 per cent of Thenfadiol hydrochloride in an isotonic buffered aqueous vehicle. It comes in half-ounce sample and one ounce trade bottles with separate dropper caps.

Dr. E. E. Campaigne, in the chemistry laboratories of Indiana University, was the first to prepare Thenfadiol, known chemically as N, N-dimethyl-N'-(3-phenyl)-N-(2-Pyridyl) ethylenediamine.

The new combination solution of Thenfadiol with Neo-Synephrine was clinically evaluated in patients with common colds, sinusitis, allergic rhinitis including hay fever, and acute coryza. Tests were conducted by otolaryngologists and allergists in a large series of cases. According to a summation by Dr. Rice, medical director, there was prompt and prolonged decongestion in all cases; repeated doses did not reduce the consistent effectiveness of the solution. There were no reports of trepidation, insomnia or restlessness. Essential freedom from central nervous system stimulation was noted.

Manner of use in the clinical studies included drops, spray and nasal pack in dosages of 2-5 cc three times a day, 1-3 cc daily and 1-2 cc daily, respectively.

Basis of the new use of Thenfadiol with Neo-Synephrine is the fact that antihistaminic compounds may benefit nasal allergy when applied nasally. Thenfadiol blocks the congestive action of histamine, and Neo-Synephrine shrinks the nasal mucosa. Action of the decongestant, widely used in nose drops, is therefore enhanced in cases where

local allergy is contributing to the symptoms.

Application may be made, Dr. Rice said, by atomizer, nebulizer, tempon or droplet installation. In most cases, the solution has produced decongestion of the nasal mucosa, using one to three cc daily in divided doses.

Thenfadiol has a high antihistaminic potency. Neo-Synephrine is Levo-a-hydroxy-B-methylamino-3-hydroxy ethylbenzene, a sympathomimetic amine closely related to epinephrine and ephedrine. Neo-Synephrine, it has been noted in numerous reports in scientific journals, produces a sustained vasoconstriction. It rarely causes burning, stinging or smarting, physicians have found.

Neo-Synephrine can be repeated more freely than ephedrine, according to studies made at the Sterling-Winthrop Research Institute, because it usually does not have deleterious reactions on the heart. In addition, it is stated, Neo-Synephrine does not cause secondary engorgement of the mucosa.

## ORETON

**ORETON VIAL 100 mg. per cc.** *Manufacturer:* Schering corporation, Bloomfield, New Jersey. *Action Constituent:* Testosterone propionate, U. S. P., in sesame oil. *Actions:* Exhibiting all of the androgenic effects of testosterone propionate, this high dosage form is intended especially as a convenient form for intramuscular administration of large amounts of the hormone where indicated. *Indications:* Female breast carcinoma, certain types of arthritis, and other conditions in both male and female where high doses of androgens are required. Provides high dosage in a small volume of menstruum. *Dosage:* Palliation of breast carcinoma; 100 mg. three times weekly by intramuscular injection. Also used in high dosages by some investigators in the treatment of rheumatoid arthritis. *How Supplied:* Multiple dose vials of 10 cc., containing 100 mg. per cc. Boxes of 1 vial.

## MEDICAL DIRECTOR

Broad expansion in Ames Company, Inc.'s product development

program has made it possible for Dr. R. L. Conklin to continue unassisted in carrying out the increased burden involved in his position as Research and Medical Director, as well as a Director of the corporation. Dr. Max Gilbert joined Ames Company February 1 as Medical Director, with Dr. Conklin continuing as Research Director in addition to his other duties.

Dr. Gilbert has a broad background in the pharmaceutical and drug industry. For eight years he

was assistant professor of chemistry at Marquette University, teaching organic chemistry and biochemistry. He received his M.D. at the Northwestern University School of Medicine in 1932, serving his internship and holding a residency at St. Luke's Hospital in Chicago. For eight years he served in the Medical Department of the Schering Corporation and later was employed as Medical Director by Wm. R. Warner Company and by Billhuber-Knoll Corporation.

#### AIR FORCE MEDICAL SERVICE ESTABLISHES CLINICAL CLERKSHIPS FOR STUDENTS

The U. S. Air Force Medical Service has established position vacancies for 75 clinical clerkships at Air Force base hospitals for medical students who have completed their junior year at medical school and who hold Air Force Reserve commissions.

To be eligible for selection as a clerk, the student must be a member of the Volunteer or Organized Air Reserve. Students selected will enter on active duty as officers in the reserve rank they now hold, with full pay and allowances. Officers who hold aeronautical ratings will not be on flying status while on duty as clinical clerks.

Point credits toward promotion and retirement in the Air Force Reserve will be given for the days on duty. Assignment to duty as a clinical clerk will be for a period not to exceed ninety days.

Clinical clerks will perform preliminary physical examinations, writing of case histories, and other similar duties under the constant supervision and instruction of Air Force medical officers. In addition, the medical student will gain a knowledge of military medicine and a picture of the structure of the Air Force Medical Service.

Further information may be obtained upon written request from the Commanding General, Continental Air Command, Mitchel Air Force Base, New York, Attention: Surgeon; or from the Office of The Surgeon General, Headquarters, United States Air Force, Washington 25, D.C.

#### AF MEDICAL SERVICE TO GRANT RESERVE COMMISSIONS UNDER ROTC

Graduates of medical, dental, pharmacology and veterinary colleges who participate in the medical ROTC program of the U. S. Army may now receive commissions in the Medical Service, U. S. Air Force Reserve according to a recent agreement between the Army and the Air Force.

Prior to the agreement, it was necessary for students in these categories who preferred reserve commissions in the Air Force to accept commissions in the Army, and then request transfer.

**Lady out of the Dark**

The selective cerebral action of Norodin is useful in dispelling the shadows of mild mental depression. The reported advantages of Norodin over chemically related analeptics include smaller dosages, more prompt and prolonged mental stimulation, and relatively few side effects. Norodin can be used to advantage in achieving the sense of well-being essential to effective patient management in functional and organic disturbances. In obesity, Norodin is useful in reducing the desire for food and countering the low spirits associated with the rigors of an enforced diet.

*Supplied: 2.5 and 5 mg. tablets in bottles of 100*

**Norodin®**  
Hydrochloride  
brand of methamphetamine hydrochloride  
PSYCHOMOTOR STIMULANT AND ANTI-DEPRESSANT  
**Endo®**

Endo Products Inc., Richmond Hill 18, N.Y.

The new agreement provides that 20 per cent of the students taking medical ROTC training may receive reserve commissions in the U. S. Air Force Medical Service. This may be increased to 30 per cent should that number of students signify a desire to apply for Air Force commissions.

Students in these fields now participating in the first and second year advanced ROTC course are to make a statement of choice of service prior to May 1, 1950.

In all future medical ROTC classes, choice of service will be stated by students when application is made for the advanced course, senior division, with the Professor of Military Science and Tactics directing the ROTC courses at the various schools.

By joint agreement, the Air Force is now furnishing and will continue to furnish officers to staff approximately 20 per cent of medical ROTC instructors. The medical ROTC program is administered by the Department of the Army.

At present, 49 medical colleges, 18 dental colleges, six veterinary colleges, and four pharmacology colleges have ROTC programs.

Students may obtain full information from the Professor of Military Science and Tactics in their college or university; or, upon written request, from the Surgeon General of the Army or Air Force, Washington 25, D. C.

#### PRENOLON AND PRENOLON ACETATE

*Manufacturer:* Schering Corporation, Bloomfield, New Jersey. *Active Constituents:* Prenolon; Schering's brand of pregnenolone in aqueous suspension. Prenolon Acetate; Schering's brand of pregnenolone acetate in oil. *Action:* Use in the treatment of rheumatoid arthritic patients has resulted in cases of increased joint mobility, less pain, greater endurance and heightened sense of well being, although individual responses to treatment have varied greatly. No toxic effects have been reported. *Indications:* Preliminary studies by prominent clinical investigators reveal definite improvement after treatment with Prenolon or Prenolon Acetate in a significant percentage of patients

suffering from rheumatoid arthritis, ankylosing spondylarthritis (Marie-Strümpell) and other collagen diseases. *Dosage:* Rheumatoid arthritis or ankylosing spondylarthritis (Marie-Strümpell): 50 to 300 mg. of Prenolon or Prenolon Acetate daily by intramuscular injection, depending on requirement and response of patient. *How Supplied:* Prenolon: 10cc. vials aqueous suspension of free pregnenolone containing 100 mg. per cc. Prenolon Acetate: 10 cc. vials sesame oil solution of pregnenolone acetate containing 50 mg. per cc.

#### NATIONAL CAMPAIGN BEGUN TO PROMOTE NEOCURTASAL

Sodium-Free Salt Substitute Being Made Available at Drug Store Fountains in Shakers, Unit Packets.

A nation-wide campaign has been launched by Winthrop-Stearns, Inc., to promote the use of Neocurtasal, a sodium-free salt substitute, at drug store soda fountains throughout the country for the benefit of those who have been directed by their physicians to abstain from the

#### new and different salt substitute

...tastes like salt  
looks like salt  
sprinkles like salt

co-salt

congestive heart failure

hypertension

toxemias of pregnancy

IN

Professional Samples  
Upon Request

Available:  
2 oz. shaker  
top package  
8 oz. economy  
package

Accepted for advertising in  
the Journal of the American  
Medical Association.

Casimir Funk Laboratories, Inc.  
affiliate of U. S. VITAMIN CORPORATION  
250 E. 43rd St. • New York 17, N.Y.



Diets  
that  
invite  
liver  
damage  
•

The heavy drinker, the erratic eater, the appetite-apeeker eat too little of the foods that contain liver-protective protein and B-vitamins. Clinical experience proves that these deficiencies can be corrected by a high protein diet—a diet supplemented by

**MEOVITE®**

Each capsule contains 250 mg. dl-methionine, 5 mg. thiamine hydrochloride, 2.5 mg. riboflavin, 25 mg. niacinamide.

*Wyeth* Incorporated, Philadelphia 3, Pa.





THE  
**velvety softness**  
THAT IS KIND TO THE BOWEL

In the treatment of constipation, Kondremul contributes a velvety soft colloidal emulsion of microscopically fine particles which mix intimately with the dry fecal residue—easing elimination and encouraging regular bowel habits.

*To meet various types of constipation,  
Kondremul is supplied in three forms:*

**KONDREMUL** Plain (containing 55% mineral oil)

**KONDREMUL** with non-bitter Extract of Cascara  
(4.42 Gm. per 100 cc.)

**KONDREMUL** with Phenolphthalein—.13 Gm. (2.2  
grs.) phenolphthalein per tablespoonful



**KONDREMUL**

*... an emulsion of Mineral  
Oil and Irish Moss*

**THE E. L. PATCH COMPANY**  
STONEHAM, MASS.



*It takes more*  
*than a balanced diet!*

Every growing child needs a diet balanced as to calorie, protein and vitamin requirements. But, often, a theoretically correct diet may actually be vitamin deficient. For instance, the child may eliminate habitually certain foods; or digestive disturbances may interfere with assimilation. Improper or excessive cooking also will dissipate certain vitamins. A continued mild vitamin deficiency can result in fatigability, irritability, skin eruptions, susceptibility to colds and infections.

**DABS Armour (improved formulae)**

the balanced vitamin capsules, supply needed supplementary vitamin administration. DABS contain a vitamin mixture similar to that contained in a high-grade vitamin-rich diet, plus liver extract.

Each DABS (improved formulae) capsule contains:

Vitamin A.....	10,000 U.S.P. Units (2½ M.D.R.)
Vitamin D.....	1,000 U.S.P. Units (2½ M.D.R.)
Vitamin B <sub>1</sub> .....	5.0 Mg. (5 M.D.R.)
Vitamin B <sub>2</sub> .....	10.0 Mg. (5 M.D.R.)
Vitamin C.....	75.0 Mg. (2½ M.D.R.)
Niacin Amide.....	50.0 Mg. (M.D.R. Not Estab.)
*Pyridoxine HCl (Vit. B <sub>6</sub> ).....	0.25 Mg.
*Calcium Pantothenate.....	5.0 Mg.
Secondary Liver Fraction.....	0.5 Gram

M.D.R. — Minimum Daily Requirement.

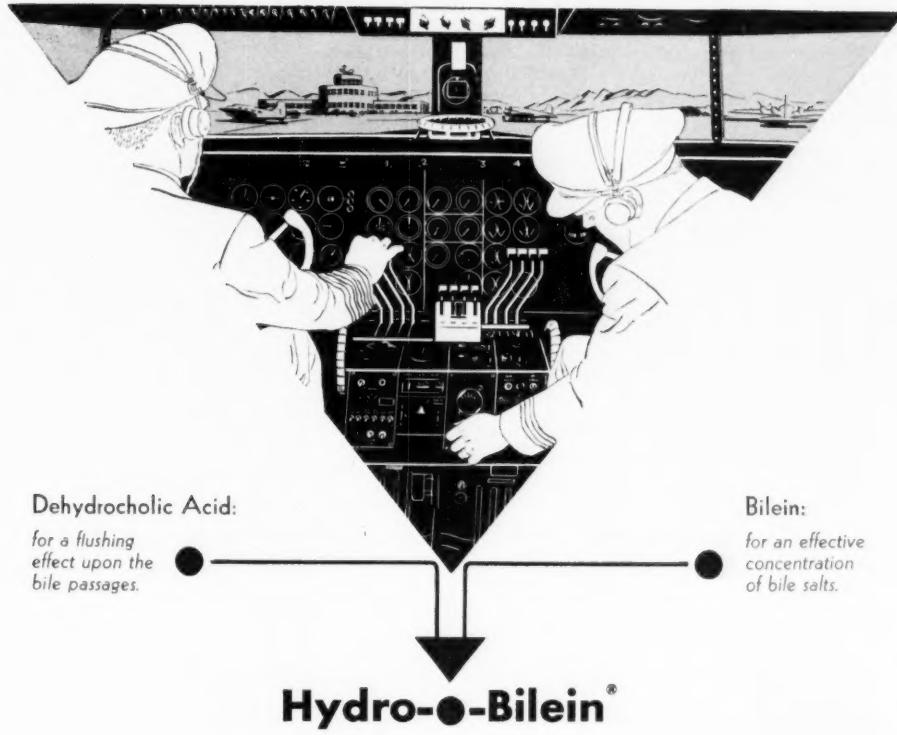
\*Need in human nutrition not yet established.

Have confidence in the preparation you prescribe—specify "Armour."



**ARMOUR**  
*Laboratories*

HEADQUARTERS FOR MEDICINALS OF ANIMAL ORIGIN • CHICAGO 9, ILLINOIS



(BILEIN® AND DEHYDROCHOLIC ACID, ABBOTT)

## *Effective alone . . . better together*

► You have prescribed dehydrocholic acid. You have prescribed the natural bile salts. Now, for greater effectiveness, for a wider range of therapy, both are combined in a single preparation, HYDRO-BILEIN. Each tablet contains 2 grs. dehydrocholic acid and 2 grs. dried fresh ox bile. Administered in this form, their separate functions complement each other—the one sluicing out inspissated bile or products of inflammation, the other stimulating the production of bile solids which aid in the absorption of fat and fat-soluble vitamins. Together they facilitate gall bladder emptying and increase intestinal motility. The average dose is one tablet two to four times daily, preferably after meals. Dosage may be reduced if it produces an undesired laxative effect. Your pharmacy has HYDRO-BILEIN in bottles of 100 and 1000 sugar-coated tablets.

**Abbott**

use of ordinary table salt for various reasons.

To stimulate this campaign for immediate patient availability, W. E. Sowersby of the Sales Division for Winthrop-Stearns has announced a complete merchandising program for Neocurtasal available to individual retailers and to chain drug stores. This promotion includes the 2-ounce shaker for counter use, attractive fountain strip signs and menu tabs noting the availability of this sodium-free salt substitute, individual packets for one-meal use and special display cartons of six 2-oz. shakers.

"Tests in spot cities last year revealed enthusiastic interest and wholehearted cooperation on the part of retailers," Mr. Sowersby said, "and we see that such a campaign will advance the relationship between the public which requires a salt-free diet and the fountain managers who make Neocurtasal available to them."

Neocurtasal is now being offered

in small unit packets which contain enough salt-substitute for the average meal. Travelers and institutions will find these packets especially convenient. Neocurtasal also comes in 8-oz. bottles.

This product is indicated "for salt (sodium)-free diets in cardiac diseases, particularly when associated with edema, hypertension, arteriosclerosis and fluid retention in pregnancy," according to Winthrop-Stearns Inc. It is also employed by many physicians as a part of weight reducing regimens. There are about 13,000,000 people in the United States who at one time or another require salt-free diets, medical statisticians reveal.

#### NOTICE

L. W. Frohlich and Company, Inc., specialists in medical advertising, have been appointed agency for the Dental Division of Johnson & Johnson. Julian Farren is Account Executive.

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**Every physician  
should see this!**

Drop a Syntrogel tablet in water. In a matter of seconds it will "fluff up" to several times its size—proof of instant disintegration—tremendous increase in adsorptive surface. This is why Syntrogel relieves "heartburn" and hyperacidity so quickly.

HOFFMANN-LA ROCHE INC. • NUTLEY 10 • N. J.

**Syntrogel®**

**Roche'**

Each Syntrogel tablet contains aluminum hydroxide, calcium carbonate, magnesium carbonate and Syntropin® "Roche."



**A Handsome Permanent Binder for the American Journal of Digestive Diseases.**

**Only \$2.00**

Made of a good grade imitation leather, holds 12 issues, one year. Easy to bind in a few minutes in your own home. Stamped on backbone with year and volume number. When ordering it is advisable to give thickness of each full year's issues.

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Please send \_\_\_\_\_ binders of The American Journal of Digestive Diseases for the years \_\_\_\_\_ Will remit \$ \_\_\_\_\_ in 10 days or return binders at your expense.

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## Vital Fluids

Decholin Sodium®, long a *clinical synonym* for hydrocholeretic effect, also has increasingly-recognized value in connection with two other vital fluids.

**Enhancement of Diuresis.** In cardiac decompensation with hepatic engorgement, Decholin Sodium given alone produces mild diuresis. More often it is administered simultaneously with mercurial diuretics to potentiate their action and reduce their dose.

**Blood Circulation Time.** Arm-to-tongue blood circulation time is reliably and relatively safely determined by injection of Decholin Sodium into a cubital vein. If desired, an arm-to-lung time test is readily included in the procedure by adding ether to the Decholin Sodium injection.

# Decholin Sodium

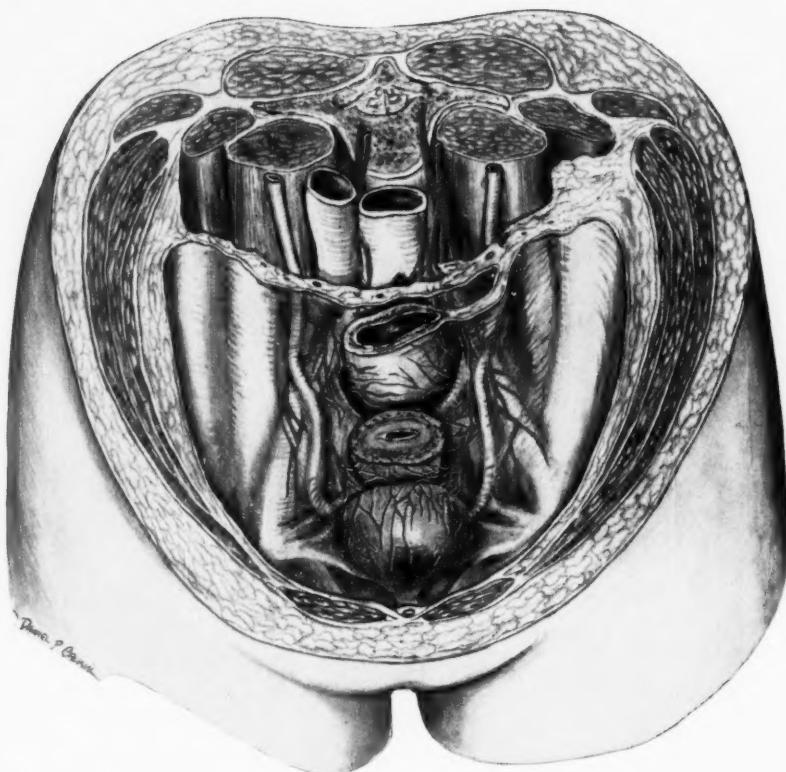
## sodium dehydrocholate

supplied in 20% aqueous solution for intravenous administration. Available now in ampuls of 3 cc., 5 cc. and 10 cc.; boxes of 3 and 20 ampuls.

The booklets, "Decholin Sodium in Blood Velocity Determination" and "The Diuretic Action of Decholin Sodium" are now available—and will be sent upon your request.



AMES COMPANY, INC.  
ELKHART, INDIANA



**In painful spasm of the upper  
and lower bowel, uterus and bladder:**

The potent antispasmodic-sedative, Pavatrine® with Phenobarbital, provides neurotropic, musculotropic and central nervous system sedative actions to prevent or to relax smooth muscle spasm. Pavatrine with Phenobarbital has shown its effectiveness in cardiospasm, pylorospasm, spasm of the sphincter of Oddi, spastic states of the colon, gastric hypermotility, dysmenorrhea due to excessive uterine contractions and bladder spasm.

**PAVATRINE** with PHENOBARBITAL  
( $\beta$ -diethylaminoethyl fluorene-9-carboxylate hydrochloride)

RESEARCH IN THE SERVICE OF MEDICINE **SEARLE**